Asymmetric Transfer Hydrogenation Reductions Using Tethered Ruthenium (II) Catalysts

By

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Declaration.

The research shown in this thesis is an account of my own independent research, unless otherwise stated. These studies were carried out at the Department of Chemistry, University of Warwick between October 2007 and September 2011. The research reported in this thesis has not been submitted, either wholly, or partially for a degree at any other academic institution.

Some of this work has appeared in the scientific literature in the following publications:

1. Parekh, V.; Ramsden, J. A.; Wills, M. *Tetrahedron: Asymmetry*, **2010**, *21*, 1549-1556.
2. Parekh, V.; Ramsden, J. A.; Wills, M. *Catal. Sci. Technol.*, **2012**, DOI: 10.1039/c1cy00364j.

Abbreviations.

δ_C	^{13}C-NMR chemical shift (ppm)
δ_H	^{1}H-NMR chemical shift (ppm)
$[\alpha]_D$	optical rotation
Å	Angstroms
Ac	acetyl
ACN	acetonitrile
AcOH	acetic acid
AcOK	potassium acetate
Ar	aryl group
ATH	Asymmetric Transfer Hydrogenation
atm	atmospheric
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
bipy	2,2'-bipyridine
[BMIM]PF_6	1-butyl-3-methylimidazolium hexafluorophosphate
Boc	di-*tert*-butyl dicarbonate
bp	boiling point
br s	broad singlet
Bu	butyl
^{t}Bu	tertiary butyl
c	concentration
CDA	chiral derivatizing agent
conv.	conversion
Cp*	pentamethylcyclopentadiene
d	doublet
DABCO	1,4-diazobicyclo[2.2.2]octane

DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
dd	doublet of doublets
dec.	decomposition temperature
DFT	density function theory
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxy ethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPEN	1,2-diphenyl ethylenediamine
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
ESI	electrospray ionization
Et_3N	triethylamine
Et_2O	diethyl ether
EtOH	ethanol
FA	formic acid
GC	gas chromatography
HCl	hydrochloric acid
HCOONa	sodium formate
hrs	hours
HPLC	high performance liquid chromatography
HR MS	high resolution mass spectrometry
IPA	isopropanol
IR	infra red
J	coupling constant (Hz)
lit.	literature

LR MS	low resolution mass spectrometry
m	multiplet
m	meta
M^+	molecular ion
M	mol dm^{-3}
Mp	melting point
m/z	mass to charge ratio
Me	methyl
MHz	Megahertz
min	minutes
MPV	Meerwein-Ponndorf-Verley
Ms	mesyl
MsCl	methanesulfonyl chloride
NMR	nuclear magnetic resonance
o	ortho
oct	octet
o/n	overnight
p	para
P	Pressure
Ph	phenyl
PMA	phosphomolybdic acid
ppm	parts per million
^{i}Pr	isopropyl
^{i}PrOK	potassium isopropoxide
^{i}PrONa	sodium isopropoxide
psi	pound-force per square inch
q	quartet

quin	quintet
rt	room temperature
s	singlet
S/C	substrate to catalyst ratio
t	triplet
T	temperature
TBAB	tetrabutylammonium bromide
TBDPSCl	*tert*-butyldiphenylchlorosilane
t or *tert*	tertiary
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TS	transition state
Ts	toluenesulphonyl
TsCl	4-toluenesulfonyl chloride
TsCYDN	N-((*p*-toluenesulfonyl)-1,2-cyclohexanediamine
TsDPEN	1,2-diphenyl-N-(p-toluenesulfonyl)ethylenediamine
TsOH	tosylic acid
tt	triplet triplet
UV	ultraviolet
ν_{max}	wavenumber (cm^{-1})
v/v	volume to volume ratio

Abstract.

By asymmetric transfer hydrogenation, substituted quinolines, which are generally regarded as challenging substrates for reduction, were successfully converted into tetrahydroquinolines using “tethered” Ru(II) and “tethered” Rh(III) complexes in formic acid/triethylamine.

An ether-linked “tethered” catalyst was successfully synthesized through a sequence that avoids the use of a Birch reduction for the formation of a 1,4-cyclohexadiene moiety. The ether link is incorporated between the basic amine of the ligand and the η^6-arene ring, giving results comparable to the alkyl-“tethered” complexes.

N-alkylated complexes containing a straight-chain substituent attached to a hydroxyl, ether or ester function can act as effective catalysts for the reduction of ketones, and also contains the required functionality for attachment of the catalyst to a heterogeneous support.

1. Introduction.

1.1 Chirality.

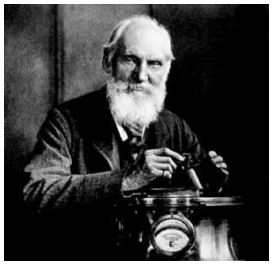


Figure 1. Lord Kelvin (William Thomson), Professor of Natural Philosophy in the University of Glasgow from 1846-1899.

The term chirality is derived from the Greek word for hand (cheir), which is a mathematical approach to the concept of "handedness"-the existence of left/right opposition, and was coined by Lord Kelvin in his Baltimore lectures on molecular dynamics and the wave theory of light in which he stated "*I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself*". Human hands are perhaps the most universally recognized example of chirality: The left hand is non-superimposable mirror image of the right hand and no matter how the two hands are oriented, it is impossible for all the major feature of both hands to coincide (Figure 2).[1]

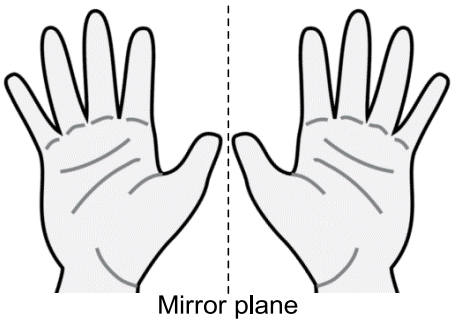
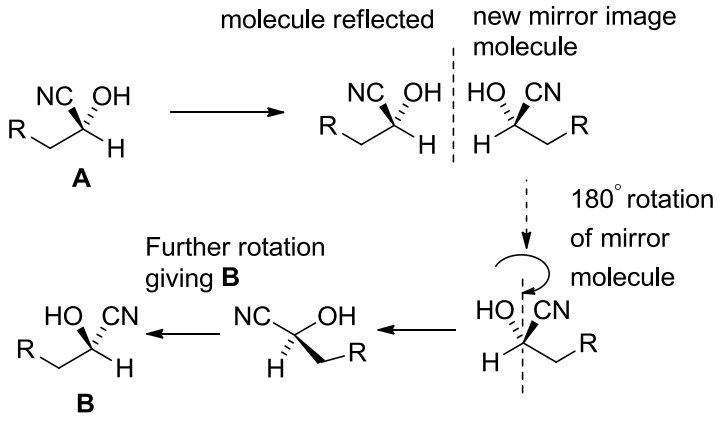


Figure 2. Human hands, an example of chirality.

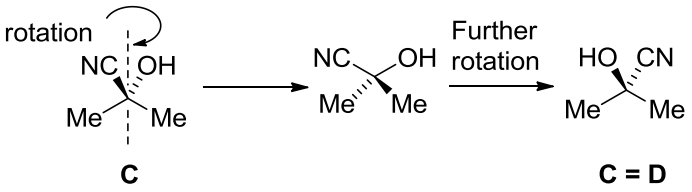
In the context of chemistry, two structures that are not identical, but are mirror images of each other are called enantiomers (Scheme 1). Enantiomers are a type of isomer called stereoisomers, as the isomers differ not in the connectivity of the atoms, but only

in the overall shape of the molecule. Structures that are not superimposable on their mirror image, and therefore can exist as two enantiomers, are called chiral.



Scheme 1. Enantiomers of cyanohydrin from the reaction between an aldehyde and cyanide.

Structures that are superimposable on their mirror images are called achiral (Scheme 2). The essential difference between the two examples shown is symmetry. Acetone cyanohydrin has a plane of symmetry running through the molecule, whereas the aldehyde cyanohydrin has no plane of symmetry, and it cannot have a plane of symmetry, because it contains a tetrahedral carbon atom carrying four different groups: OH, CN, RCH_2 and H. Such a carbon atom is known as a stereogenic centre or chiral centre.[1]



Scheme 2. Achiral structures of acetone cyanohydrin.

Structures that have more than one stereogenic centre can give rise to stereoisomers that that are not mirror images of one another called diasteroisomers. Two diastereoisomers

are different compounds meaning their physical and chemical properties are different, and have different relative stereochemistry. Diastereoisomers maybe achiral (Figure 3) or chiral (Figure 3).[1]

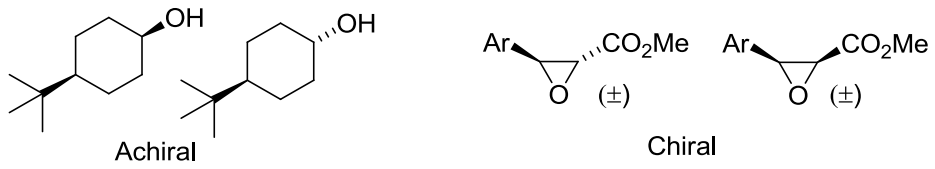


Figure 3. Achiral and chiral diastereoisomers.

Enantiomers have identical NMR spectra, IR spectra, physical and chemical properties in the absence of an external chiral influence meaning the same melting point, boiling point, solubility properties and chromatographic retention times. The single exception is the ability of the enantiomers to rotate plane-polarized light. We call the enantiomer that rotates plane-polarized light to the right (gives a positive rotation) the (+)-enantiomer (or the d: *dextrorotatory* enantiomer) and the enantiomer that rotates plane-polarized light to the left (gives a negative rotation) the (-)-enantiomer (or the l : *laevorotatory* enantiomer).

The direction in which light is rotated is not dependent on whether a stereogenic centre is *R* or *S*. An (*R*) compound is equally as likely to be (+) as (-), if it is (+) then its (*S*) enantiomer must be (-). Observation of the rotation of plane-polarized light is known as polarimetry and it is calculated by using the following equation: $[\alpha] = \alpha$ (angle through which the light is rotated by) / l (path length in dm) x c (in g/100 cm^3) and the light usually used is from a sodium lamp (symbol $_D$ is used to represent this) with a wavelength of 589 nm. If the angle is very small then mercury lamp with a wavelength of 546 nm can be used for this purpose. The specific rotation [α] value obtained can be used as a guide to the enantiomeric purity of a sample, in other words to how much of

each enantiomer it contains, specific rotation values are usually used for comparison with known literature values in order to confirm the configuration of the enantiomers obtained. Chiral derivatizing agent[2] (CDA) for e.g. Mosher's acid can be used to determine enantiomeric excess and configuration of simple chiral amines and alcohols as it can convert a mixture of enantiomers into diastereoisomers, which means it can then be possible to distinguish them using NMR. X-Ray crystallography is most commonly used to determine the configuration of novel chiral compounds. The way in which *R*/*S* is assigned to each stereocentre or *E* (*trans*)/*Z* (*cis*) is assigned to each double bond is by the Cahn-Ingold-Prelog priority rules. For the assignment of *R*/*S*, each of the four substituents around the chiral centre is given a priority number. Atoms with higher atomic numbers get higher priority. If two (or more) of the atoms attached to the chiral centre are identical, then the priority number is assigned by assessing the atoms attached to those atoms. The molecules are then arranged so that the lowest priority substituent is pointing away from you. If you move in a clockwise manner from highest to the second lowest assigned substituent, then the chiral centre is given the label *R* (for *rectus*, Latin for right), and if you are moving in an anticlockwise manner then the chiral centre is given the label *S* (for *sinister*, Latin for left). The procedure is very similar when assigning *E*/*Z*, but in this case if two higher groups are *cis*, the alkene is *Z* (from the German *zusammen*, means together), and if they are *trans* the alkene is *E* (from the German *entgegen*, means opposite).[1]

1.2 Biological significance of chirality.

All proteins, enzymes, amino acids, carbohydrates, nucleosides and a number of alkaloids and hormones are chiral compounds. In contrast to chiral artificial products, almost all (some are racemic or made in both forms) natural compounds are under single enantiomeric form, for example, all natural amino acids are *L*-isomer and all

natural sugars (carbohydrates) are *D*-isomers. The D/L notation (a very old convention), not to be confused with d: dextrorotatory and l: laevorotatory, is derived from the signs of optical rotation of *R* and *S* glyceraldehyde respectively (Figure 4), with D-glucose being the natural enantiomer, and L-glucose the unnatural enantiomer.

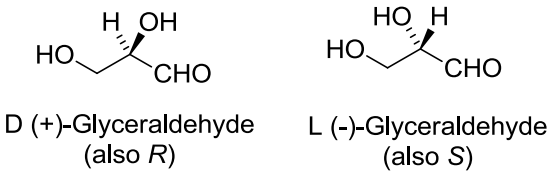


Figure 4. Illustration of glyceraldehyde with D-(natural)/L-(unnatural) and *R*/*S* notations.

Amino acids are classified in to L-(natural) and D-(unnatural), with most L-amino acids being of *S*-configuration (Figure 5).

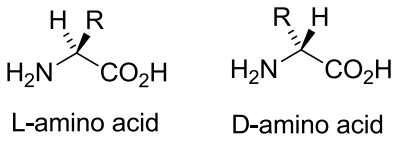


Figure 5. Amino acids classified in to L-(natural) and D-(unnatural).

Although the chemical and physical properties for enantiomers in the absence of an external chiral influence are the same, most enantiomers of drugs exhibit marked differences in biological activities such as pharmacology, toxicology, pharmacokinetics and metabolism when exposed to a chiral surrounding. For example thalidomide **1**, which was marketed as the racemate led to a tragedy in the 1960s in Europe. The sedative-hypnotic drug thalidomide exhibited irreversible neurotoxicity and teratological (mutagenic) effects in which babies were born deformed. The drug was prescribed to pregnant women to counter morning sickness. Studies showed that these effects were caused by the (*S*)-enantiomer and that the (*R*)-enantiomer contained the

desired therapeutic activity. More recently studies were concluded that both enantiomers of thalidomide are unstable and spontaneously epimerize to form the racemate *in-vivo* in humans (Figure 6).[3a]

Albuterol (salbutamol) **2** is sold as a racemate, and is the leading bronchodilator, which is a β_2-adrenergic receptor agonist that can increase bronchial airway diameter without increasing heart rate. The bronchodilator activity resides in (*R*)-albuterol also known as levosalbutamol which is sold as the trade name xopenex. The (*S*)-albuterol enantiomer is not inert as it indirectly antagonizes the benefits of (*R*)-albuterol and may have proinflammatory effects. These are pharmacokinetic differences between the enantiomers with (*S*)-albuterol being cleared more slowly. The (*S*)-enantiomer tends to accumulate in preference to the therapeutically effective (*R*)-enantiomer. Levosalbutamol sold as the single (*R*) enantiomer has the same bronchodilator activity as racemic albuterol, but has a superior side-effect profile (Figure 6).[3a,3b]

Parkinson's disease sufferers are treated with the non-proteinogenic amino acid DOPA **3**. DOPA is chiral, and only (*S*)-DOPA (known as *L*-DOPA) is effective in storing nerve function. The active form of the drug is an achiral compound dopamine which is formed by decarboxylation of **3** and is used to increase dopamine concentrations and dopamine-responsive dystonia, but it cannot cross the blood-brain barrier to reach the site of action. (*S*)-DOPA can and is then decarboxylated by the enzyme dopamine decarboxylase to dopamine. This enzyme however is not able to metabolize (*R*)-DOPA (known as *D*-DOPA), and so to prevent the build-up of (*R*)-DOPA which could prove to be fatal, it is essential that DOPA is administered pure as the (*S*)-enantiomer (Figure 6).[3b]

Bupivacaine **4**, currently the most widely used long acting local anaesthetic agent in both surgery and obstetrics has a good safety record, but its use has resulted in fatal cardiotoxicity, usually after accidental intravascular injection. The single (*S*)-enantiomer version of bupivacaine called levobupivacaine was introduced, which has clinically equivalent anaesthetic potency to bupivacaine, but with reduced CNS and cardiotoxicity. Due to the differences observed in biological activities for different enantiomers of drugs, all chiral forms of a drug are tested rigorously for possible side effects and for chiral stability *in vivo* before approval (Figure 6).[3a,3c]

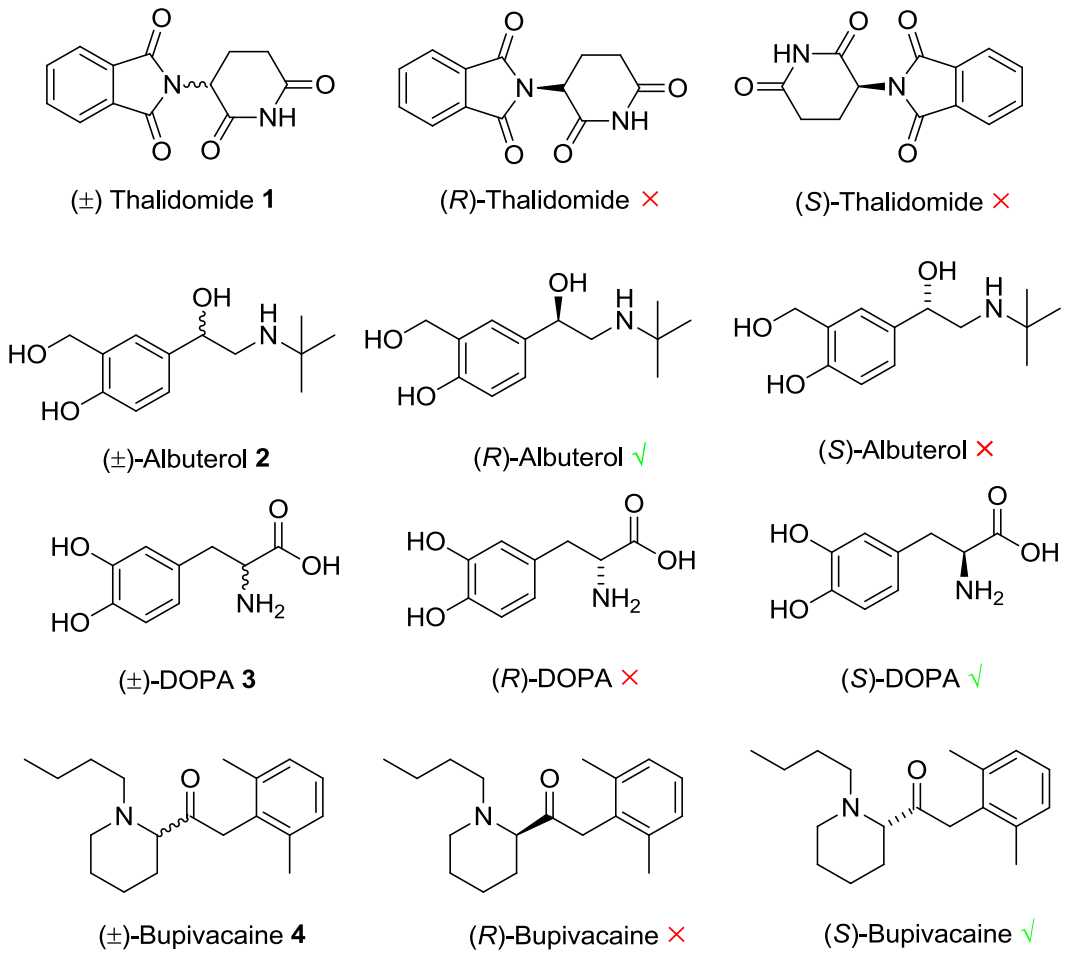


Figure 6. Examples of chiral drug molecules, with the tick representing the active enantiomer, and cross representing the toxic enantiomer.

1.3 Asymmetric catalysis.

In order to understand the concept of asymmetric reactions you have to focus on the two transition states for the formation of *R* and *S* enantiomers. In a racemic reaction, where an achiral reagent is reacted with an achiral molecule, the transition states of both *R* and *S* enantiomers are of equal energy ($\Delta G^{i} = \Delta G^{ii}$), therefore both *R* and *S* enantiomers are produced in equal amounts to yield a racemic product. In an enantioselective reaction the catalyst used (or reagent) facilitates one of the transition states to be at lower energy than the other as shown in Figure 7 (a reminiscent of an enzyme-catalysed biological reaction). The catalyst interacts with an achiral substrate (the type of substrate used is also important) in the transition state which has lowered in energy by $\Delta\Delta G^{\#}$ from ΔG^{i} and in this case it favours the formation of the (*R*)-enantiomer, whereas transition state for the formation of the (*S*)-enantiomer may remain unaffected or may increase or decrease (not decrease too much) in energy. The value of $\Delta\Delta G^{\#}$ plays a crucial role in determining the selectivity of the reaction.

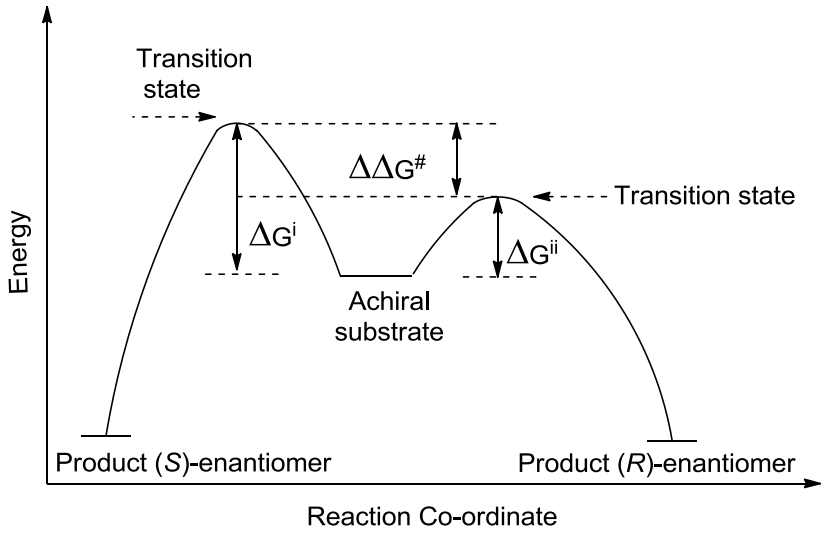
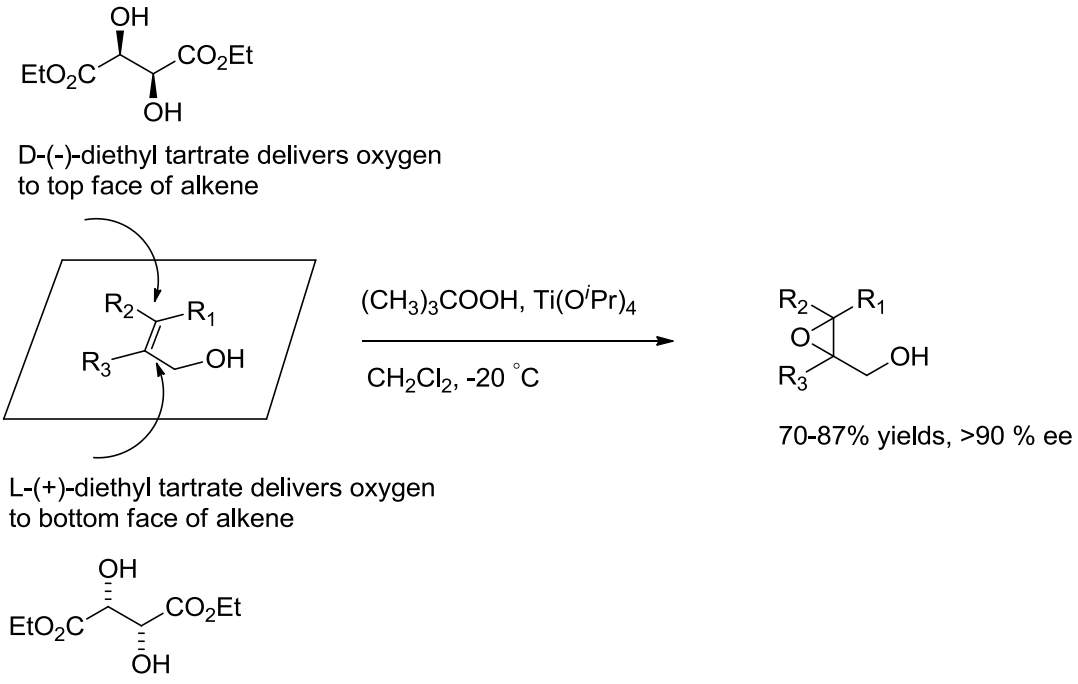


Figure 7. Reaction coordinates for the asymmetric synthesis of chiral substrate.

The use of catalysts proves to be very economical as very low quantities of catalyst (less than 1 mol%) is usually required in an asymmetric catalysis reaction and the catalyst can also be isolated after a reaction and reused. Some established asymmetric catalytic reactions will now be reviewed.

1.3.1 Sharpless epoxidation.

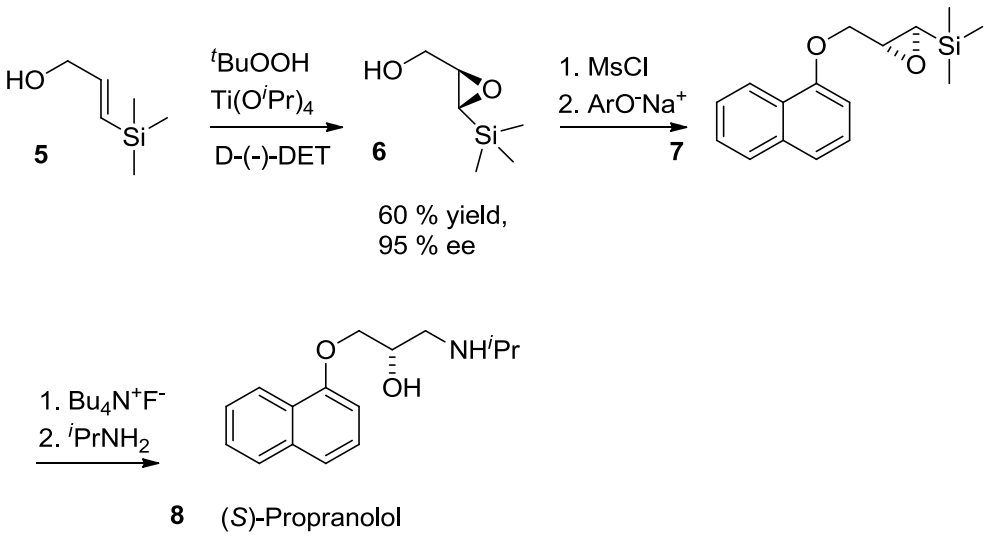
The Sharpless epoxidation reaction is an enantioselective chemical reaction to prepare 2,3-epoxyalcohols from primary and secondary allylic alcohols. It was discovered in 1980 by Barry K. Sharpless and Tsutomu Katsuki. The simplicity of this metal-catalysed asymmetric epoxidation is what makes this method so attractive, as the necessary components (+) or (-)-diethyl tartrate, titanium tetraisopropoxide and *tert*-butyl hydroperoxide are all commercially available at low to moderate cost (Scheme 3).



Scheme 3. Asymmetric synthesis of 2,3-epoxyalcohols.

This chiral epoxidation system possesses two key features; first of all it gives uniformly high asymmetric inductions throughout a range of substitution patterns in the allylic

alcohol substrate. Secondly depending on the tartrate enantiomer used, the system is able to deliver the epoxide oxygen from the same enantioface of the olefin regardless of the substitution pattern. As illustrated in Scheme 3 the use of (+)-diethyl tartrate leads to addition of the epoxide oxygen from the bottom face, and using (-)-diethyl tartrate as expected from the top face. Transition-metal-catalysed epoxidations work only on allylic alcohols, so there is one limitation to the method because the coordination of an alcohol to the titanium metal is crucial for the reaction to take place. An example of where Sharpless epoxidation has been employed is for the synthesis of propranolol, which is a sympatholytic non-selective beta blocker and is used to treat hypertension, anxiety and panic. Not many target molecules are themselves epoxides, but one of the great advantages of epoxides is its high versatility, meaning they can react with many types of nucleophiles to give 1, 2-disubstituted products.[4a]



Scheme 4. Synthesis of (*S*)-propranolol **8** with the use of Sharpless epoxidation.

The most obvious starting material for this synthesis, allyl alcohol itself gives an epoxide which is hard to handle. So Sharpless instead used the silicon-substituted allylic alcohol **5** for the asymmetric epoxidation step giving **6** in 60 % yield and 95 % ee. The

hydroxyl group was mesylated and displaced with 1-naphthoxide to give **7** and then after treatment with fluoride to remove the silicon, the epoxide was opened with isopropylamine to give (*S*)-propranolol **8** (Scheme 4).[4b]

1.3.2 Hydroboration.

In 1981, Itsuno reported the asymmetric reduction of aromatic ketones utilizing the borane complexes of chiral amino-alcohols (**9-12**, Figure 8) derived from α-amino-acids to give secondary alcohols with up to 60% ee.[5a] Application of such complexes for asymmetric reduction was first reported by Fiaud and Kagan[5b] who used borane-chiral amine complexes derived from ephedrine in the reduction of ketones but obtained very low ee (3.6 – 5.0%). Attempts were also made to use the borane complexes with (*R*)-(+)-, (*S*)-(-)-α-methylbenzylamine, or α-amino-esters in the presence of $BF_3.Et_2O$ in asymmetric reductions of ketones but limited success was achieved (ee of up to 20%).

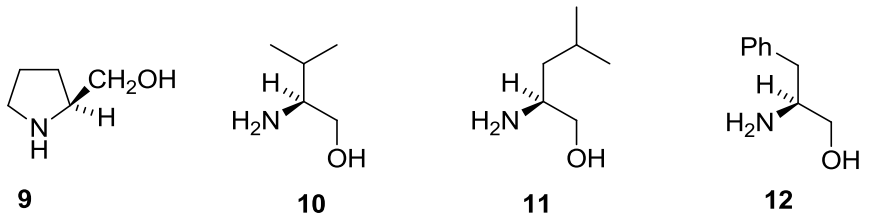
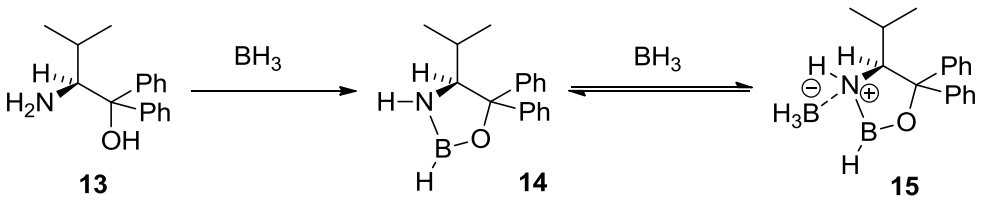


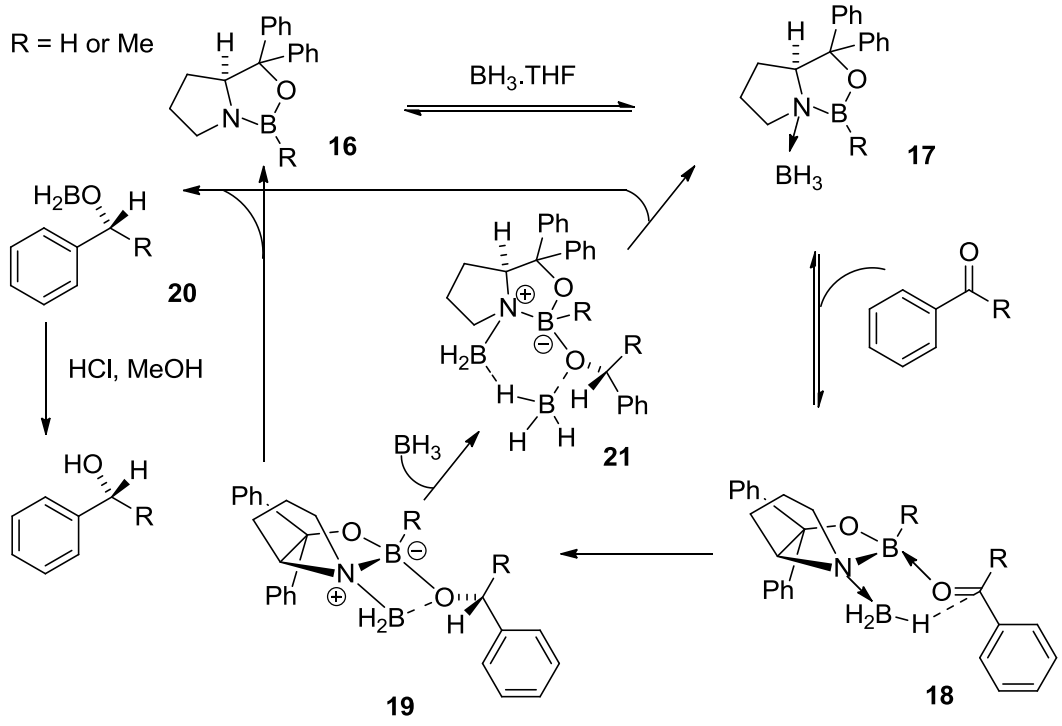
Figure 8. Chiral amino-alcohols used for the formation of chiral alkoxy-amine-borane complexes.

In 1983 after 2 years, Itsuno reported very high selectivities for the reduction of aromatic ketones (94 – 100 %) by using the new chiral borane complex **14** prepared from (*S*)-(-)-2-amino-3-methyl-1, 1-diphenylbutan-1-ol **13** and borane (Scheme 5).[5c-5e]



Scheme 5. Itsuno's chiral amine-borane system for asymmetric reduction of ketones.

Soon after, Corey extended the idea and developed the 1,3,2-oxazaborolidines **16** (Scheme 4) as a new generation of homochiral reduction catalysts, which rapidly reduces ketones with up to 97 % ee in the reduction of acetophenone.



Scheme 6. Proposed mechanism for the catalytic enantioselective reduction of ketones by oxazaborolidines **16**.

Corey and co-workers had proposed the reaction mechanism shown in Scheme 6, to explain the selectivity obtained in the catalytic reduction. The first step involves the coordination of the reducing agent BH_3 with the Lewis basic nitrogen atom of **16**, this causes the activation of the BH_3 as a hydride donor and also enhances the Lewis acidity

of the catalyst's endocyclic boron. Subsequently, the endocylic boron of the catalyst coordinates to the ketone at the sterically more accessible electron lone pair (i.e. the lone pair closer to the smaller substituent). This preferential binding in **18** acts to minimize the steric interactions between the ketone (the large substituent directed away) and the R group of the catalyst, and aligns the carbonyl and the coordinated borane for a favourable, face-selective hydride transfer through a six-membered transition state **18**. Hydride transfer then yields chiral boron enolate **20**, which upon acidic work-up yields the chiral alcohol. Dissociation of the reduction product from **19** may occur by two different pathways: 1) reaction of the alkoxide ligand attached to the endocylic boron atom with the adjacent boron atom of **19** to regenerate **16** and form the borinate **20** by cyclo-elimination; or 2) by the addition of BH_3 to **19** to form a six-membered BH_3-bridged species **21**, which decomposes to produce the catalyst-BH_3 complex **17** and borinate **20**.[5f]

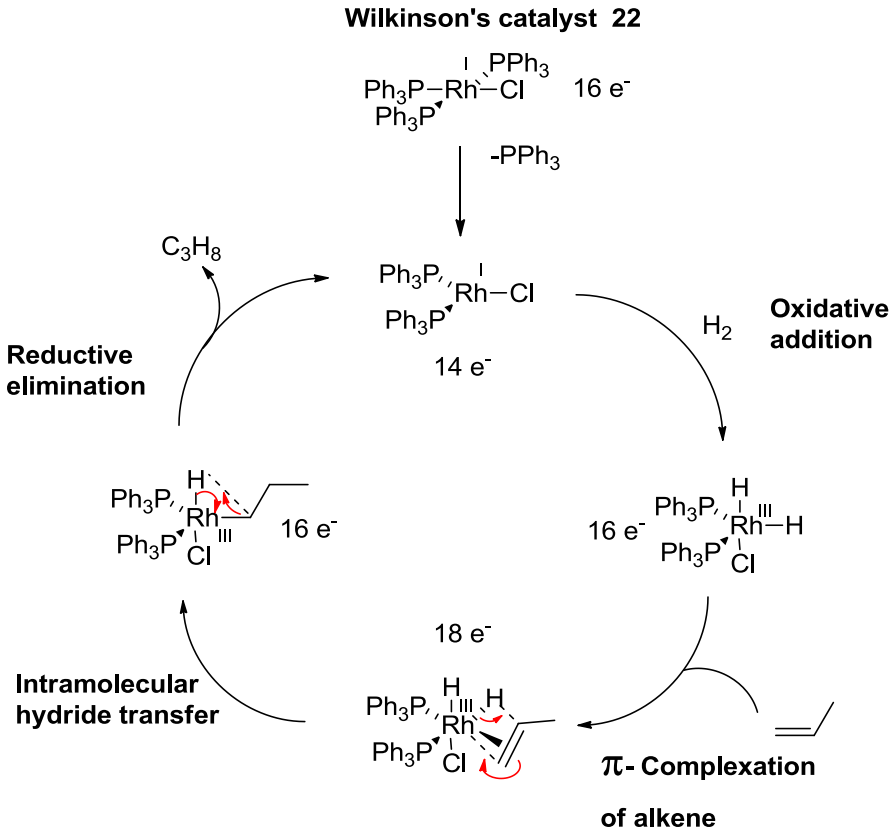
Oxazaborolidines are excellent homogeneous catalysts for the enantioselective reductions of prochiral carbonyl compounds and have gained significant synthetic utility in the synthesis of a significant number of natural products, including lactones, terpenoids, alkaloids, steroids and biotins.[5f, 5g, 5h]

1.3.3 Asymmetric Hydrogenations.

1.3.3.1 Wilkinson's Catalyst.

Asymmetric hydrogenation plays an important role in today's synthesis world. In 1966 Sir Geoffrey Wilkinson who received the Nobel Prize in 1973 for his work on organometallic compounds introduced the first example of homogeneous catalysis. Chlorotris(triphenylphosphine)rhodium(I) known as the Wilkinson's catalyst $[RhCl(PPh_3)_3]$ **22** (Scheme 7) is able to catalyse the hydrogenation of simple unhindered

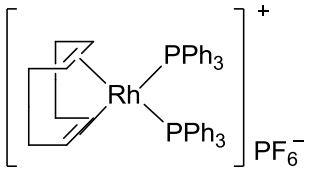
alkenes in organic solvents rapidly under mild conditions.[6a] The mechanism of Wilkinson's catalytic system is reasonably well-established, and it involves the initial dissociation of one or two triphenylphosphine ligands to give 14 e^- or 12 e^- complexes, respectively, followed by oxidative addition of H_2 to the metal. Subsequent π-complexation of alkene, intramolecular hydride transfer (olefin insertion), and reductive elimination results in extrusion of the alkane product as shown in Scheme 7. The reaction rates are dependent on the steric hindrance of the substrates.[6b, 6c]



Scheme 7. Catalytic hydrogenation of propylene.

1.3.3.2 Schrock-Osborn catalyst.

The Schrock-Osborn catalyst **23** (Figure 9), discovered in 1976 by 2005 Nobel Prize winner Richard R. Schrock and John Osborn, who carried out his doctoral study with Sir Geoffrey Wilkinson, is another example of a homogeneous catalyst for hydrogenation reactions and is more active than Wilkinson's catalyst due to the cationic metal centre being more electrophilic, favouring alkene coordination, which is often the rate determining step.[6d]

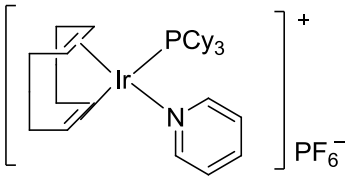


Schrock-Osborn catalyst
23

Figure 9. Schrock-Osborn catalyst.

1.3.3.3 Crabtree's catalyst.

In 1979 Professor Robert H. Crabtree developed an iridium based complex with 1,5-cyclooctadiene, tris-cyclohexylphosphine and pyridine also known as Crabtree's catalyst **24** (Figure 10) while working on iridium analogues of the Wilkinson's rhodium-based catalyst.



Crabtree's catalyst
24

Figure 10. Crabtree's catalyst.

Crabtree's catalyst is another homogeneous catalyst for hydrogenation reactions and is more active than the Schrock-Osborn catalyst and at least 100 times more active than Wilkinson's catalyst. Crabtree's catalyst is also able to reduce tri- and tetra substituted alkenes, which the Wilkinson's catalyst and the Schrock-Osborn catalyst are unsuccessful in reducing (Table 1). It also gives superior directing effect for cyclic substrates.[6e]

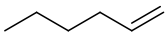
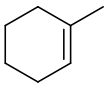
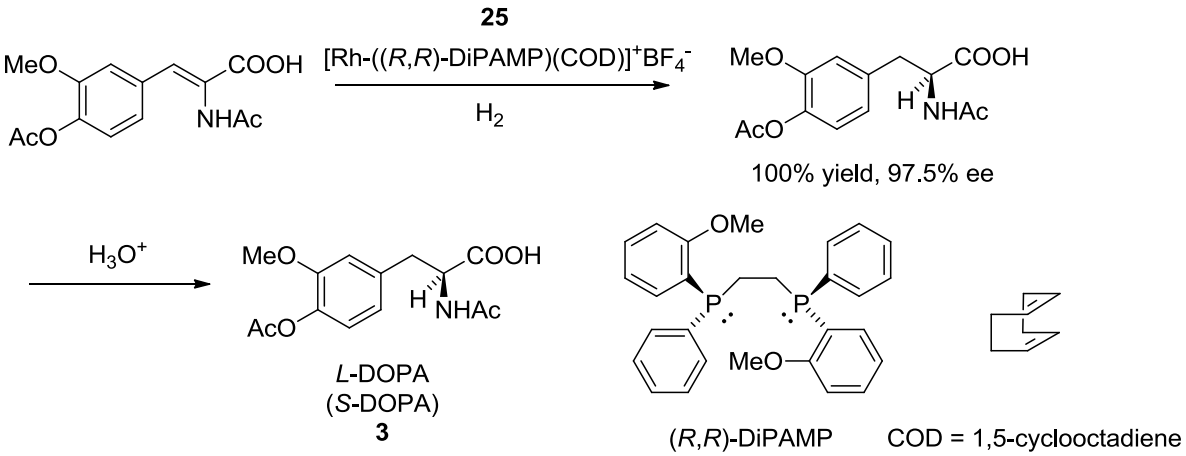
	Turnover Frequency (TOF)			
Substrate =				
Wilkinson's catalyst Benzene/EtOH, 25 °C	650	700	13	-
Schrock-Osborn Catalyst CH_2Cl_2, 25 °C	4000	10	-	-
Crabtree's catalyst CH_2Cl_2, 0 °C	6400	4500	3800	4000

Table 1. Rates (In mol of substrate reduced (mol of catalyst)$^{-1}$ h^{-1}) of hydrogenation of variously substituted olefins with active catalysts of different types.

1.3.3.4 Asymmetric Hydrogenation using DIPAMP complexes.

Since the discovery of Wilkinson's catalyst, it has inspired many research scientists to synthesise tertiary stereogenic carbon atoms by asymmetric hydrogenation of alkenes using optically active transition metal complexes. In 1977, William S. Knowles (Nobel Prize winner in 2001) and his collaborators Billy D. Vineyard and M. Jerry Sabacky discovered a bidentate C_2 symmetric version **25** of the cationic Schrock-Osborn catalyst, giving very high enantioselectivities in the hydrogenation of achiral enamides.[7a] This was the first demonstration that a chiral transition metal complex could effectively transfer chirality to a non-chiral substrate with selectivities that rival those observed in enzymes, and lead to the 1st commercialized asymmetric process for the synthesis of *L*-

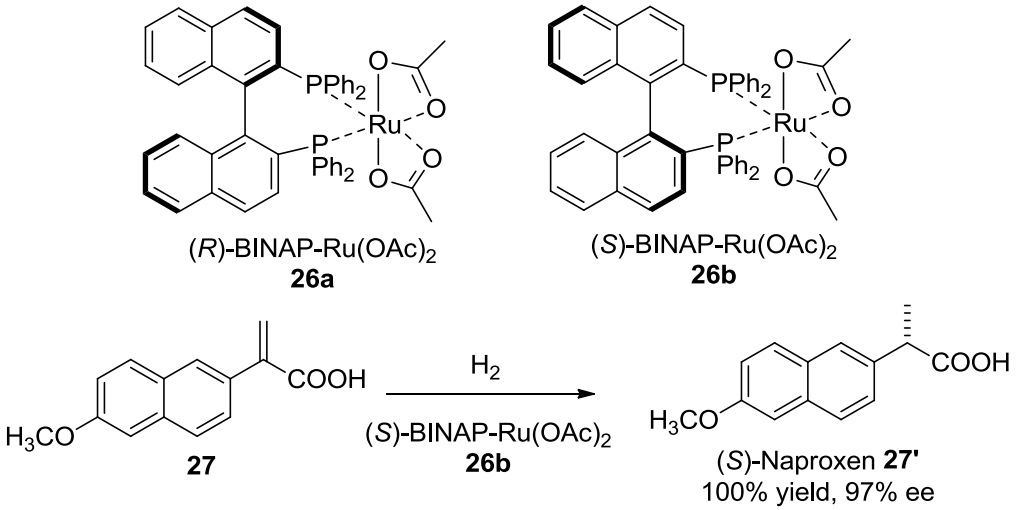
DOPA **3** (Scheme 8),[7b] a drug used for the treatment of Parkinson's disease as previously described.



Scheme 8. Monsanto research group led by Knowles established a method for the industrial synthesis of *L*-DOPA **3**.

1.3.3.5 Asymmetric Hydrogenation using Ru(II)/Rh(III)-BINAP complexes.

The discovery of BINAP-Ru complexes in the mid 1980's extensively broadened the scope of olefenic and ketonic substrates for asymmetric hydrogenation. In 1984 the axially disymmetric bis(triaryl)phosphine ligand discovered by Noyori and co-workers was first used for Rh(I)-catalysed asymmetric hydrogenations of α-(acylamino) acrylic acids and esters.[8a] The use of BINAP when combined with Ru, proved to be a successful combination for the asymmetric hydrogenation of various unsaturated substrates (C=O and C=C bonds). The synthesis of the anti-inflammatory drug naproxen **27'** was successfully carried with the use of this catalytic system, reducing the acrylic acid **27** using [(*S*)-BINAP-Ru$(OAc)_2$] **26b**, giving the product **27'** in 100% yield and 97% ee (Scheme 9).[8b]



Scheme 9. The use of asymmetric hydrogenation for the synthesis of naproxen **27'**.

Asymmetric hydrogenation using various Ru-BINAP[8c,8d], and Rh-BINAP[8e-8g] derived complexes have been successfully applied to the reduction of β-keto esters,[8h-8o] and ketones[8p,8q]

1.3.3.6 Asymmetric Hydrogenation using Ir(I) and Ru(II) complexes for the reduction of quinolines.

Optically active tetrahydroquinoline derivatives are an important class of building blocks for asymmetric synthesis in pharmaceutical and agrochemical industries and for the total synthesis of natural products (Figure 11). The (*S*)-enantiomer of flumequine **28** is an antibacterial agent of the quinolone family. Several other derivatives such as torcetrapib **29** and compound A **30**, have attracted much attention as potent inhibitors of the cholesterol ester transfer protein, which is a target for the treatment of low high-density lipoprotein cholesterol and atherosclerosis.[9a] The conversion of quinolines to tetrahydroquinolines is a useful direct method for the synthesis of chiral, non-racemic N-containing heterocycles from readily available starting materials. A number of reports on the pressure hydrogenation of quinolines have been published.[9-11]

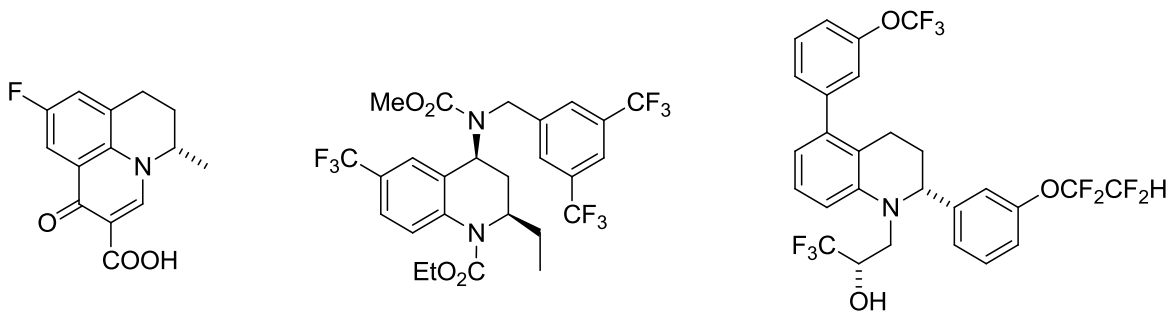
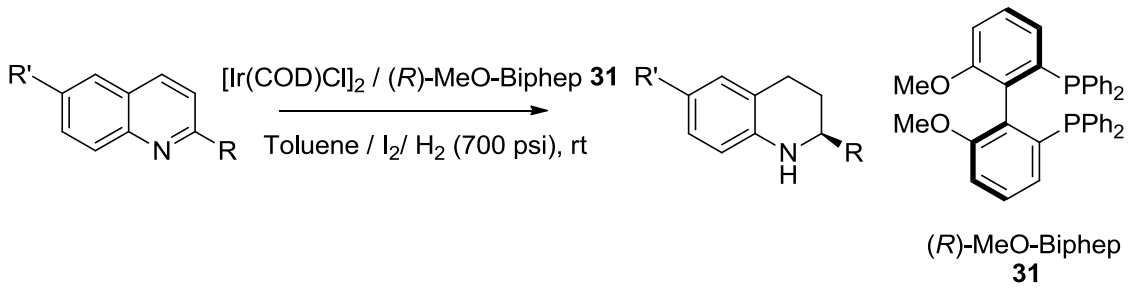


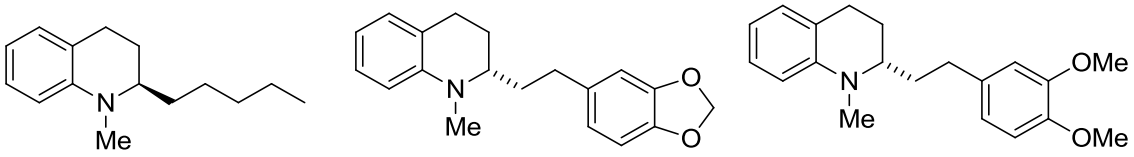
Figure 11. Examples of important 1,2,3,4-tetrahydroquinoline derivatives.

The first example reported by Zhou and co-workers in 2003 of asymmetric quinoline hydrogenation employed chiral biaryldiphosphine ligands **31** with an Ir(I) salt,[9b] and gave products with ee's of up to 96% and conversion of up to 95% (Scheme 10). Iodine was found to be an essential additive.



Scheme 10. Highly enantioselective iridium-catalyzed hydrogenation of heteroaromatic compounds, quinolines.[9b] Reaction conditions: substrate (1 mmol), $[Ir(COD)Cl]_2$ (0.5%), (*R*)-MeO-Biphep **31** (1.1%), I_2 (10%), toluene (5 cm^3), H_2 (600-700 psi), 25 °C.

This method was applied for the asymmetric synthesis of three naturally occurring alkaloids angustureine **32**, galipinine **33** and cuspareine **34** (Figure 12).



(-)-Angustrureine
94% yield
32

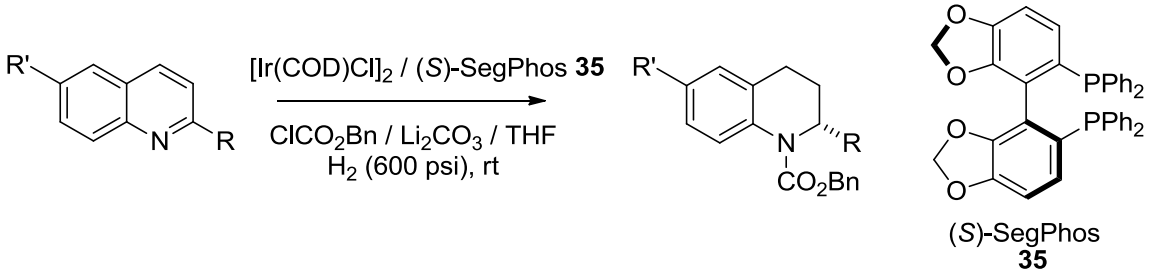
(-)-Galipinine
94% yield
33

(-)-Cuspareine
91% yield
34

Figure 12. Bioactive compounds derived from chiral 1, 2, 3, 4-tetrahydroquinoline.

A variety of iridium complexes have been reported using chiral phosphorous ligands, including diphosphines, diphosphites, monodentate phosphorous ligands, P, N ligands and other examples to catalyze the enantioselective hydrogenation of a wide range of 2-alkyl-substituted quinoline derivatives, giving good to excellent enantioselectivities. Examples of some of these ligands have been shown (Scheme 11-16).

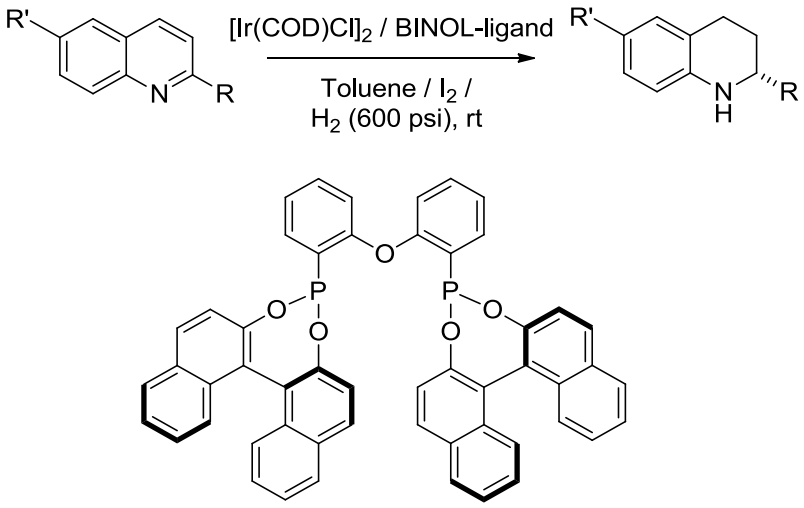
The activation of quinolines with chloroformates has been reported to improve the rates of reactions, giving up to 90% ee and 95% conversion for quinolines and up to 83% ee and 87% conversion for isoquinolines[9c] (Scheme 11).



(*S*)-SegPhos
35

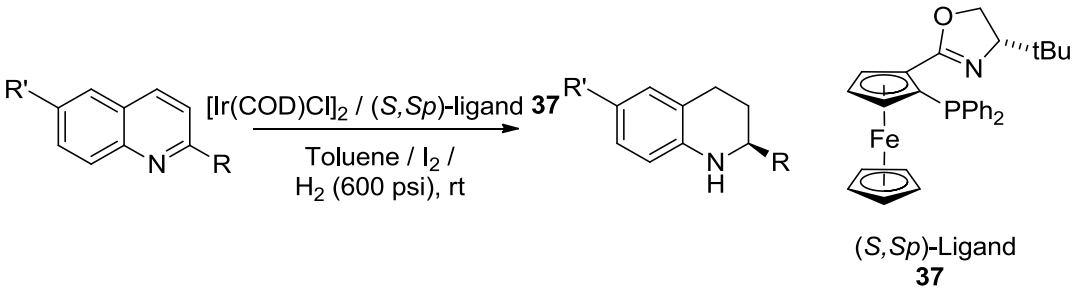
Scheme 11. AH of quinolines and isoquinolines activated by chloroformates.[9c] Reaction conditions: substrate (1.0 mmol), $[Ir(COD)Cl]_2$ (0.5%), (*S*)-SegPhos **35** (1.1%), THF (5 cm^3), Li_2CO_3 (1.2 mmol),$ClCO_2Bn$ (1.1 mmol).

Asymmetric Ir-catalyzed hydrogenation of quinolines using BINOL-derived diphosphonites **36** gave enantioselectivity of up to 96% and conversion of up to 96%, with a chiral diphenyl backbone[9d] (Scheme 12).



Scheme 12. AH of quinolines catalysed by iridium complexes of BINOL-derived diphosphonites **36**.[9d] Reaction conditions: substrate: $[Ir(COD)Cl]_2$: (*S*)-BINOL **36**: I_2=200: 1: 2: 2, H_2 (600 psi), toluene, 23 °C, 20 hrs.

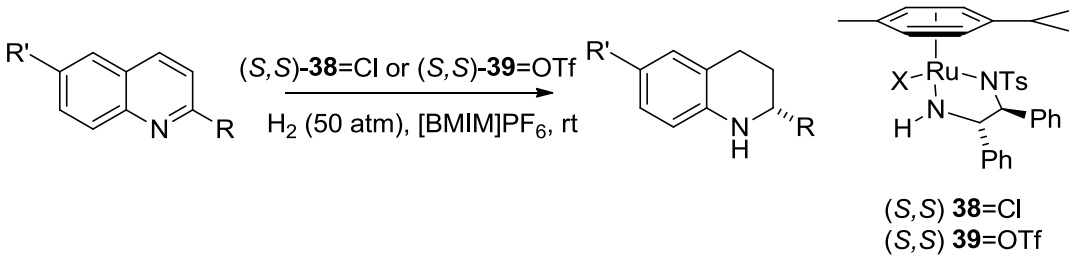
Ir complexes with chiral ferrocenyloxazoline P, N ligands **37** are effective catalysts for the AH of heteroaromatic compounds such as quinolines, and up to 92% ee was obtained with conversions up to 95% (Scheme 13). [9e]



Scheme 13. AH of quinolines catalyzed by iridium with chiral ferrocenyloxazoline derived P, N ligands **37**.[9e] Reaction conditions: substrate (1 mmol) / $[Ir(COD)Cl]_2$/chiral ligand **37**/I_2= 100/0.5/1.1/5, toluene (5 cm^3), H_2 (600 psi), rt.

The use of nitrogen-donor ligands, such as diamines, in this application is less developed. In 2006, Noyori and co-workers reported that chiral η^6-arene-TsDPEN-Ru(II) complex is not only excellent for ATH, but also for the AH reduction of aromatic

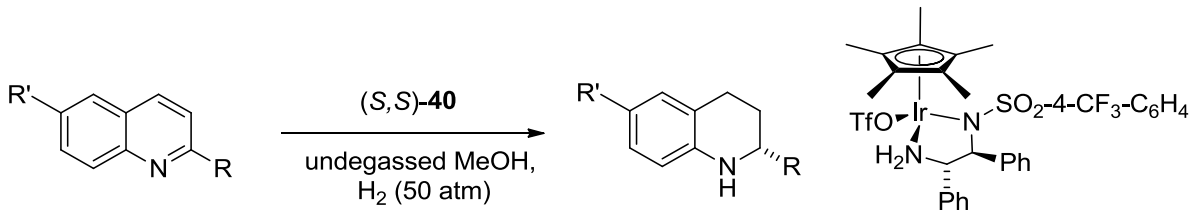
ketones.[9f] Fan and co-workers later demonstrated that the AH of quinolines using chiral η^6-arene-TsDPEN-Ru(II) complex **38** (Scheme 14) in an ionic liquid gave excellent results.[9g] In this process, the ionic liquid was essential – reactions in methanol proceeded with much lower activity.



Scheme 14. Hydrogenation of quinolines using a recyclable phosphine-free chiral cationic ruthenium catalyst.[9g] Reaction conditions: substrate (0.20 mmol) in [BMIM]PF_6 (1.0 cm^3), (*S*,*S*)-**38** (1.0 mol%), H_2 (50 atm), 25 °C, 15-24 hrs.

Quinoline substrates were efficiently hydrogenated to give tetrahydroquinolines with up to 99% ee and up to 97% conversion, without the need for additives via this first phosphine free cationic Ru/TsDPEN catalyst.[9g] The use of ionic liquid not only facilitates the recyclability, but also enhances the stability and selectivity of the catalyst.

A new kind of highly effective phosphine-free Ir-catalysts for the asymmetric hydrogenation of quinolines was developed, giving products in up to 99% ee.[9h] The reaction did not require inert gas protection throughout the entire operation, Scheme 15. The use of an acidic additive was demonstrated to be important for optimal activity. These results suggested that the reduction of quinolines was proceeding by an ionic catalytic pathway in which *N*-protonation was required to activate the hydride addition process,[9g, 9h] which was different from the mechanism of the AH of ketones.

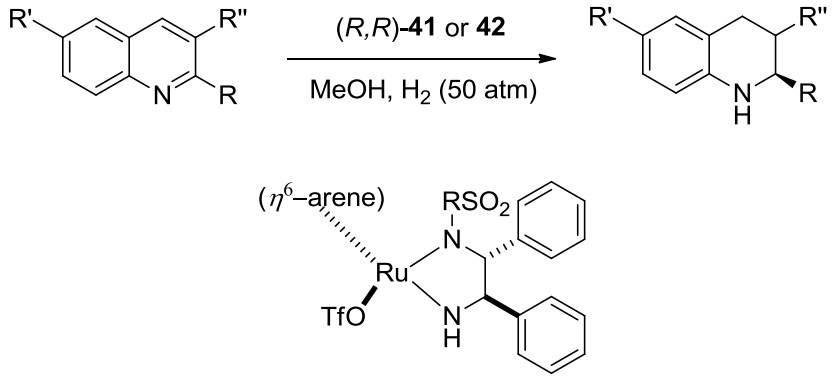


(*S,S*)-**40**

Scheme 15. Air-stable and phosphine-free iridium catalysts for highly enantioselective hydrogenation of quinoline derivatives.[9h] Reaction conditions: substrate (0.75 mmol) in undegassed MeOH (1 cm^3), (*S, S*)-**40** (0.2 mol%), TFA (10 mol%), H_2 (50 atm), 15 °C, 24-28 hrs.

Despite the significant progress made, the mechanism of quinoline reductions with these types of catalysts remained to be elucidated, in contrast to the better known asymmetric reduction of ketones. Fan and co-workers very recently reported the systematic study on the AH of a broad range of quinoline derivatives using Ru-diamine catalysts together with a detailed mechanistic study through experiments and DFT calculations.

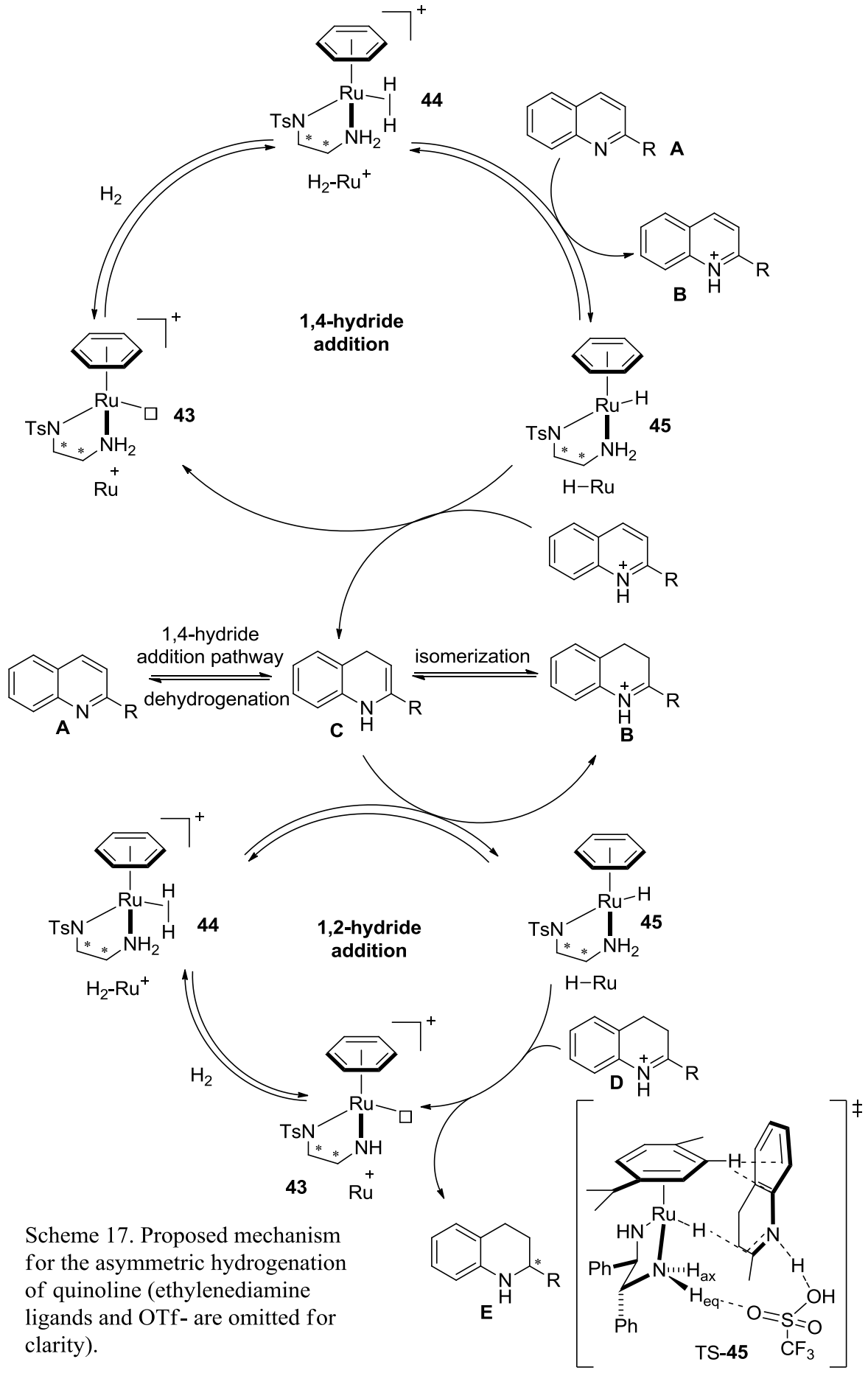
A wide range of quinoline derivatives, including 2-alkylquinolines, 2-arylquinolines, 2-functionalized and 2,3-disubstituted quinolines were efficiently hydrogenated under mild conditions with up to >99% ee and up to 5000 TON, using η^6-arene-*N*-tosylethylenediamine-Ru(II) complexes **41** and **42** (Scheme 16).[9a]



(*R,R*)-**41**: R= 4-$CH_3C_6H_4$; η^6–arene= hexamethylbenzene
(*R,R*)-**42**: R= CH_3; η^6–arene= *p*-cymene

Scheme 16. Asymmetric hydrogenation of 2-alkylquinolines, 2-arylquinolines, 2-functionalized and 2, 3-disubstituted quinolines. Reaction conditions: 0.15-0.20 mmol substrate, 1 cm^3 of MeOH/2 cm^3 EtOH (2-arylquinolines), 0.2-1.0 mol% cat, 0-25 °C, H_2 (50 atm), 12-48 hrs.

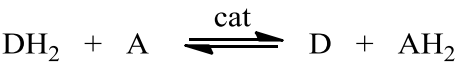
The cascade hydrogenation of quinoline occurs through an ionic instead of a concerted catalytic pathway, involving 1,4-hydride transfer, isomerization, and 1,2-hydride transfer. As illustrated in Scheme 17, the ionized ruthenium complex Ru^+ **43** reversibly accommodates a dihydrogen to form dihydrogen complex H_2-Ru^+ **44**. Deprotonation of the dihydrogen ligand **44** by quinoline **A** generates both the active Ru-H **45** species and the activated substrate **B**. A subsequent 1,4-hydride transfer affords the enamine intermediate **C** and the regenerated Ru+ **43**. Similarly, the enamine **C** serves as a base to deprotonate the dihydrogen ligand **44**, resulting in the Ru-H **45** and the iminium cation **D**. Then 1,2-hydride transfer gives the final product, 1,2,3,4-tetrahydroquinoline **E**, enantioselectively and regenerates Ru^+ **43**. The dihydroquinoline intermediate **C** can be reversibly dehydrogenated by Ru-catalyst **43** to give the quinoline **A**, while the 1,2-hydride transfer step is irreversible under the asymmetric hydrogenation conditions. The reaction between the activated iminium cation **D** and the Ru-H **45** takes place via a cyclic 10-membered transition structure TS-**45**, with the participation of TfO^- anion. Similarly to what has been shown by Noyori for ketone reductions, the enantioselectivity in this system originates from the CH/π interaction between the η^6-arene ligand in the Ru-complex and the fused phenyl ring of the dihydroquinoline.[9a]



Scheme 17. Proposed mechanism for the asymmetric hydrogenation of quinoline (ethylenediamine ligands and OTf- are omitted for clarity).

1.4 Asymmetric transfer hydrogenation

1.4.1 Traditional mechanisms



DH_2 = hydrogen donor; A = hydrogen acceptor

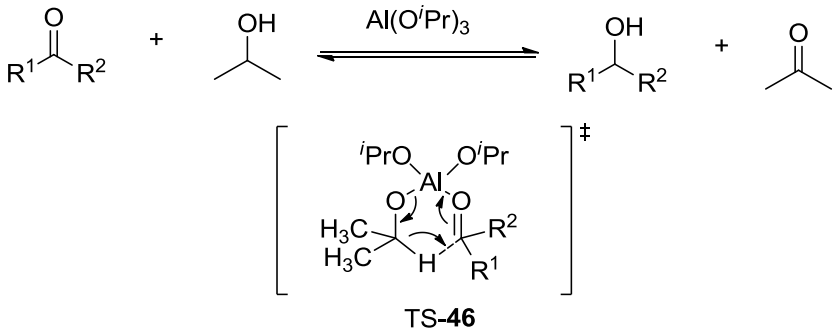
Scheme 18. Reduction of multiple bonds via transfer hydrogenation.

Transfer hydrogenation or hydrogen-transfer is the reduction of multiple bonds with the use of a hydrogen donor in the presence of a catalyst (Scheme 18). The process involves abstraction of hydrogen from the reagent (hydrogen donor) with the involvement of catalyst, followed by (or in concert with) hydride addition to the unsaturated functional group of the substrate (hydrogen acceptor). The benefits of transfer hydrogenation as opposed to pressure hydrogenation include procedural simplicity, avoidance of hazardous reagents such as molecular hydrogen and borane, as well as the need of pressure vessels (saving costs, as purchasing expensive equipment for handling these reagents is not required). In addition to this, the use of a specific hydrogen donor can favourably affect the rate and selectivity of a given reaction. However, the drawback with transfer hydrogenation is its unfavourable thermodynamics for the reduction of ketones, using alcohols, especially propan-2-ol, as hydrogen source. This means careful selection of hydrogen donor and reaction conditions are required if good conversion and ee are to be obtained.[13a-13c]

From a mechanistic point of view, transfer hydrogenation of ketones can occur via two general reaction paths: (a) concerted process called, *direct hydrogen transfer* and (b) step-wise process called, the *hydridic route*.[13a]

(a) Direct hydrogen transfer:

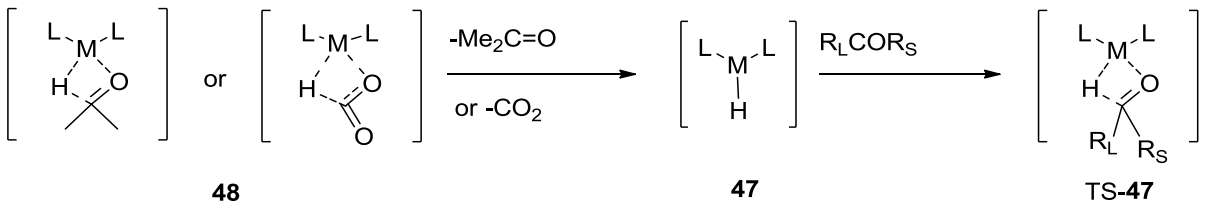
This is a concerted process, and it involves the formation of a six-membered cyclic transition state in which both the hydrogen donor (^{i}PrOH) and hydrogen acceptor (ketone) are held together in close proximity to the metal centre (TS-**46**, Scheme 19). This mechanism is similar to that proposed for the Meerwein-Ponndorf-Verley (MPV) reduction.[13d-13g]



Scheme 19. Mechanism for the Meerwein-Ponndorf-Verley (MPV) reduction.

(b) Hydridic route:

Transfer hydrogenation via the hydridic route takes place in a step-wise manner, and it involves the intermediate formation of metal hydride **47** by interaction of catalyst with hydrogen donors such as IPA and formic acid **48**, eliminating either acetone or carbon dioxide. The metal hydride **47** then undergoes hydride transfer with a coordinated ketone **TS-47** (Scheme 20).



Scheme 20. Hydridic mechanism for transfer hydrogenation of ketones.

The route taken in a particular system is dependent on the metal catalyst and hydrogen donor. Main group elements such as aluminium in the MPV reduction[13e,13f] have been reported to take the hydrogen transfer route. As oppose to this, transition metal complexes, as stated by Noyori, "prefer the hydride mechanism".[13b] An example of this is shown with $[RhH(bipy)_2]$, in the mechanism of $[Rh(bipy)_2Cl]$-catalysed dehydrogenation of ethanol in the presence of a base.[13h] Also, the involvement of a ruthenium dihydride species in a $[RuCl_2(PPh_3)_3]$ and NaOH catalyst system for the transfer hydrogenation of ketones was suggested by Bäckvall.[13i]

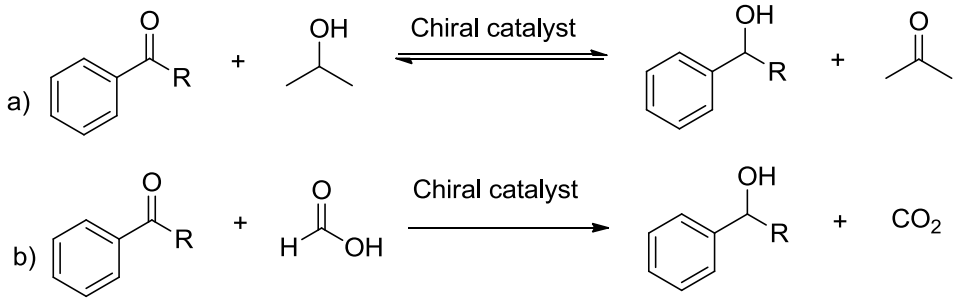
In 1991, Bäckvall reported the enhanced activity of $[RuCl_2(PPh_3)_3]$ for the transfer hydrogenation of ketones by isopropanol with the use of catalytic amount of NaOH. No transfer hydrogenation took place without base.[13i] This finding was important, as in previous ruthenium-catalysed transfer hydrogenation of ketones, the reaction took place at high temperatures.[13j,13k]

1.4.2 Hydrogen sources.

In transfer hydrogenation, one of the most common sources of hydrogen donors are secondary alcohols, in particular isopropanol. The use of isopropanol and other secondary alcohols however has the inherent problem of ketone/alcohol equilibrium, preventing high conversion being obtained. This is due to the similarity of the hydrogen source and the product; both being secondary alcohols. In effect, the reverse process may take place, where the chiral secondary alcohol (product) acts as the hydrogen donor, transferring its hydrogen and oxidising back to the starting ketone (starting material), and reducing the acetone back to isopropanol.[14a] The reverse process which can be enhanced by elongated reaction times or high substrate concentration, has frequently caused deterioration in optical purity of the chiral

product. The oxidation potential of the substrate controls the position in which the equilibrium lies,[14b] therefore 100% conversion is theoretically impossible and it is often required to use low substrate concentration to maximise the yield in the reaction. A base is normally used in transfer hydrogenation reactions, when isopropanol is utilized as the source of hydrogen (a), Scheme 21).

In recent years, formic acid/triethylamine (5:2) mixture (triethylammonium formate), which is a highly activated form of formic acid,[14c] has been used as the source of hydrogen in transfer hydrogenation reactions. The use of formic acid eradicates the problem of reversibility encountered with isopropanol, as the dehydrogenation of formic acid generates gaseous carbon dioxide which is usually released in to the atmosphere in an open system. This process is therefore irreversible, meaning complete reduction can now be theoretically achieved, and with enantioselectivity being under kinetic control. (b), Scheme 21)

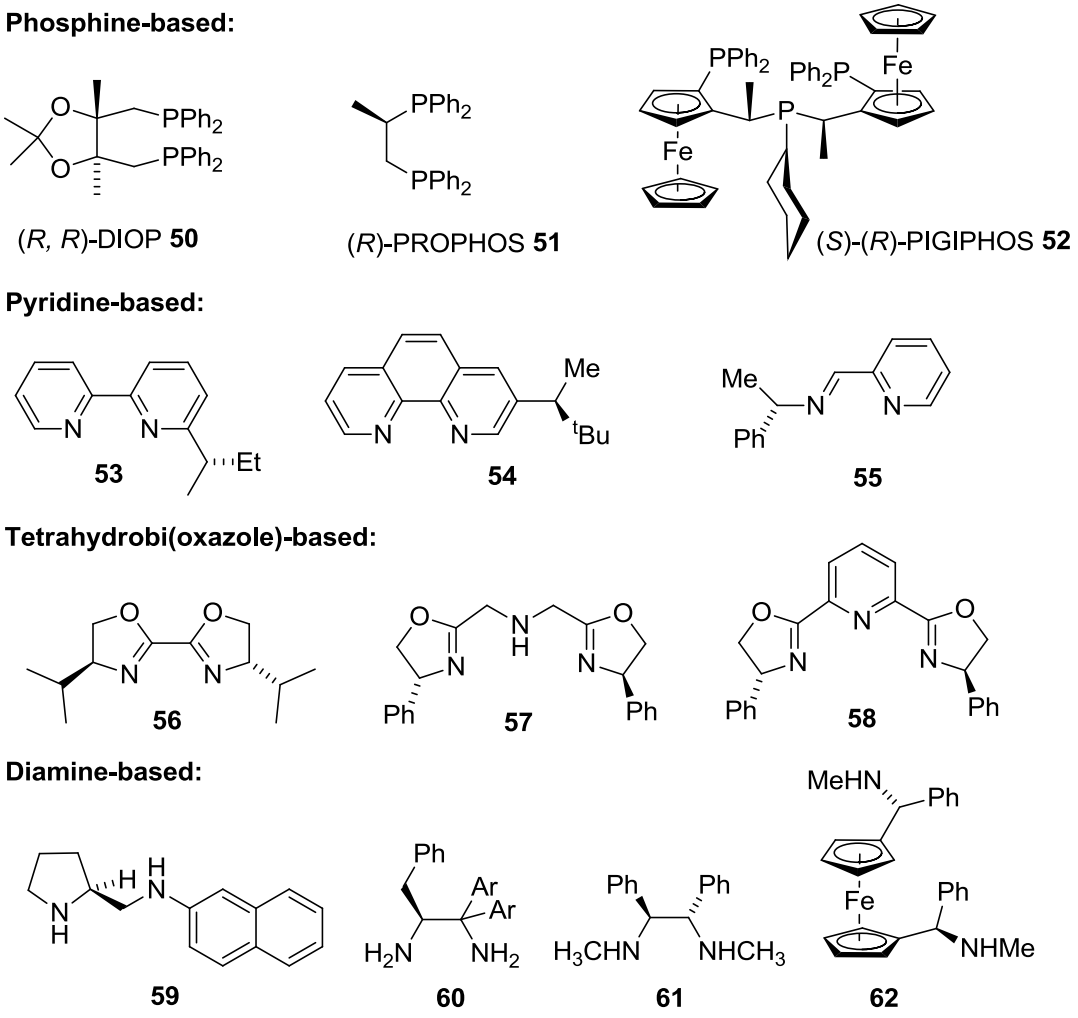


Scheme 21. Transfer hydrogenation reaction using a) isopropanol and b) formic acid as source of hydrogen.

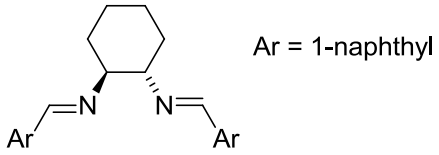
1.4.3 Ligands for Asymmetric Transfer Hydrogenation.

A general review on the more recently developed ligands used in asymmetric transfer hydrogenation will be presented. Acetophenone **49a** is usually used, unless stated, as a model substrate for comparing the reactivity of the ligands.

Throughout the years various phosphine **50-52**,[15a-15d] pyridine-based **53-55**,[15e-15g] tetrahydrobi(oxazole) **56-58**,[15h-15j] diamine **59-62**,[16a-16e] diimine **63**,[16f] BINOL-derived diphosphonite **64**,[16g] tridentate **65-69**[16h-16j, 17a-17b] and tetradentate **70-71** ligands[17c] have been used in conjunction with either Ru, Rh and Ir as ATH catalysts, giving poor to excellent enantioselectivity for the reduction of acetophenone **49a** (Figure 13).

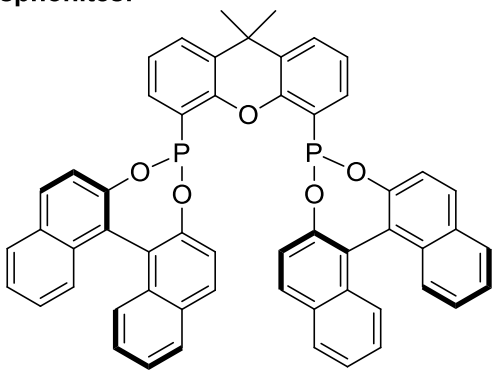


Diimine-based:



63

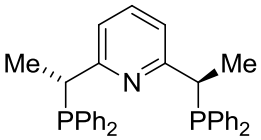
BINOL-derived diphosphonites:



64

Tridentates:

P, N, P and N, P, N



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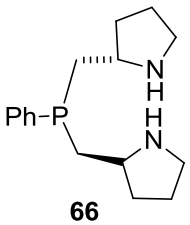

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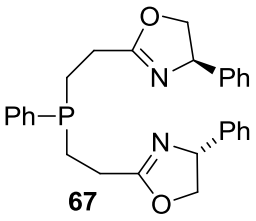

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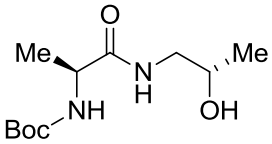
N, N, O



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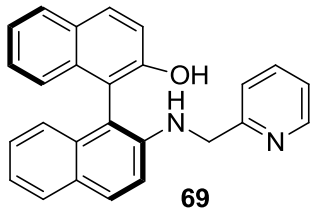

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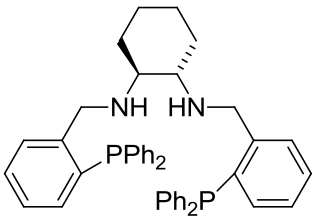
Tetradentates:

Diamine/diphosphine



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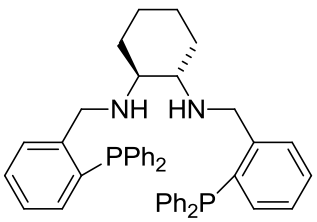

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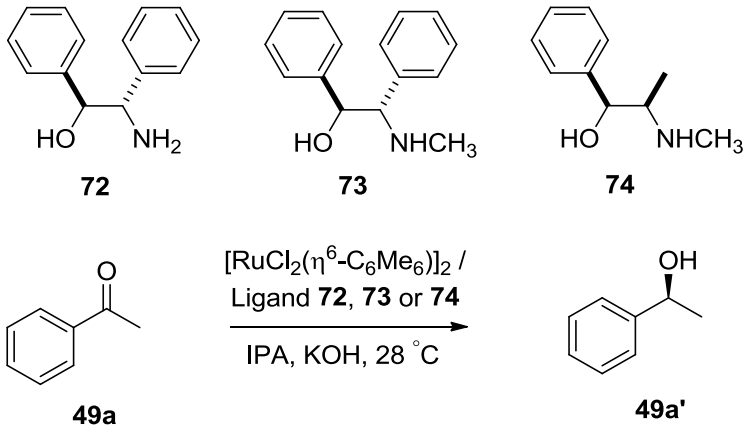
Figure 13. Types of ligands used over the years for the ATH of **49a**.

These processes could still be further improved for practical use in organic synthesis, being limited by low catalytic activity, insufficient enantioselectivity, low substrate/catalyst molar ratio (S/C), or narrow scope.

1.4.3.1 β-Amino alcohol ligands.

In 1996, Noyori and co-workers discovered that the ATH reduction of aromatic ketones, using chiral β-amino alcohols **72-74** in propan-2-ol catalysed by arene-ruthenium(II) complex showed high-ligand acceleration effects, and high enantioselectivity (Scheme 22).[17d]



Scheme 22. ATH of **49a** using Ru(II) complexes of **72**, **73** and **74**.

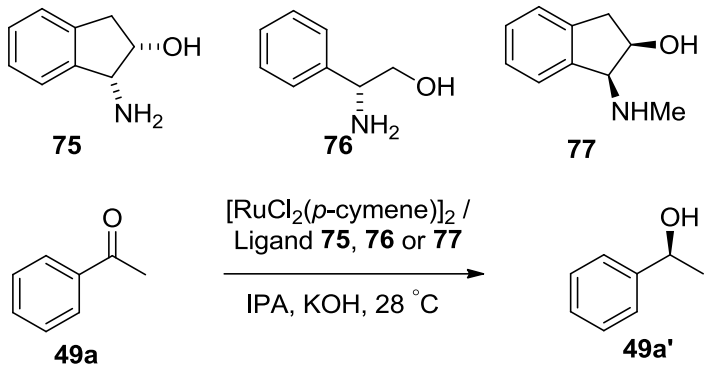
Entry	Ligand	Time (hrs)	% Yield	% ee	Configuration
1	(1*S*,2*S*)-**72**	1	96	78	*S*
2	(1*S*,2*S*)-**73**	1	94	92	*S*
3	(1*S*,2*R*)-**74**	1	95	91	*S*

Table 2. ATH of **49a** using Ru(II) complexes of **72**, **73** and **74**. Reaction was carried out at 28 °C using a 0.1 moldm^{-3} solution (5 mmol) in IPA. Ketone:Ru:ligand:KOH = 200:1:2:5.

The highest chiral efficiency (Table 2) was shown by hexamethylbenzene-(1*S*, 2*S*)-2-methylamino-1,2-diphenylethanol [(1*S*, 2*S*)-**73**], giving **49a'** in 92% ee and 94% yield after 1 hr at 28 °C. The reduction proceeded 5x faster than the reaction using

[{$RuCl_2(\eta^6$-$C_6H_3Me_3$-1,3,5)}$_2$]-(1*S*,2*S*)-*N*-(toluene-*p*-sulfonyl)-1,2-diphenylethylenediamine system which was reported by Noyori in 1995.[17e]

Intrigued by this, Wills (Scheme 23, **75**-**77**)[17f] and Anderson (Scheme 24, **78**-**80**)[17g] investigated the use of stereochemically rigid *β*-amino alcohol ligands with Ru(II) complexes, in the attempt to increase the activity of the catalyst, decrease the catalyst loading and to maximise enantioinduction for industrial applications.



Scheme 23. ATH of **49a** using Ru(II) complexes of **75**, **76** and **77**.

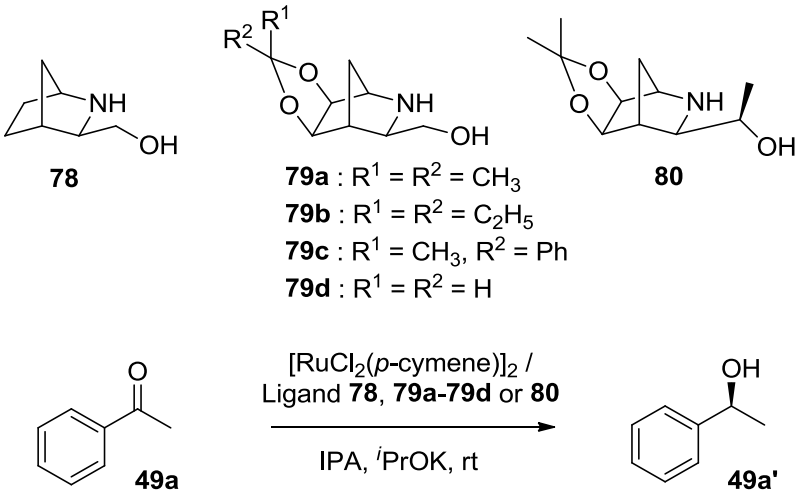
Entry	Ligand	Time (hrs)	% Yield	% ee	Configuration
1	(1*R*,2*S*)-**75**	1.5	70	91	*S*
2	(*R*)-**76**	2	95	23	*S*
3	(1*S*,2*R*)-**77**	15	33	27	*S*

Table 3. ATH of **49a** using Ru(II) complexes of **75**, **76** and **77**. Reaction was carried out at 28 °C using 1 mol% of **75**, **76** or **77**, 0.25 mol% of [$RuCl_2$(*p*-cymene)]$_2$, 2.5 mol% of KOH, IPA.

The stereochemically rigid amino alcohol **75** in conjunction with [$RuCl_2$(*p*-cymene)]$_2$ proved to be an excellent catalyst for the reduction of **49a**, giving **49a'** in 70% yield and 91% ee (Table 3, Entry 1). The results obtained for the reduction of a series of aromatic ketones under identical conditions using **75** gave the corresponding alcohols in good to excellent yield's and ee's. In contrast to this, using a non-rigid amino alcohol **76** for the reduction of **49a** did give a relatively high conversion of 95 % but quite a low ee of 23%

(Table 3, Entry 2). The importance of a primary amine group was clearly identified due to the low conv/ee (Table 3, Entry 3) obtained when **77** was employed for the ATH reduction.[17f]

A new generation of 2-azanorbornyl stereochemically rigid amino alcohol ligands were highly active for the reduction of aromatic ketones and extremely active when a ketal function was introduced into the ligands **78-80**.[17g]



Scheme 24. ATH of **49a** using Ru(II) complexes of **78**, **79a-79d** and **80**.

Entry	Ligand	Time (hrs)	% conv	% ee	Product TOF (h^{-1})
1	**78**	3	90	94	1050
2	**79a**	1	92	96	3000
3	**79b**	1	72	95	1900
4	**79c**	1	90	96	2800
5	**79d**	1	73	96	1500
6	**80**	0.25	97	96	8500

Table 4. ATH of **49a** using Ru(II) complexes of **78**, **79a-79d** and **80**. S/C = 1000

The ATH reduction of **49a** using [Ru(*p*-cymene)(**79a**)], showed an increase in conversion, ee and a threefold increase in rate when compared to [Ru(*p*-cymene)(**78**)]. The DFT studies showed that the possible explanation for this enhancement in rate is due to the presence of a dioxolane ring in **79a** which lowers the energy in the transition

state caused by van der Waals attractions between the dipole in the dioxolane ring and the dipole in the substrate. Modifications made to the substituents on the ketal group (**79b**-**79d**) did not further enhance the activity of the catalyst. However when [Ru(*p*-cymene)(**80**)] was used for the reduction of **49a**, the activity of the catalyst was far greater than [Ru(*p*-cymene)(**79a**)], giving 97% conversion, 96% ee within 25 minutes with product TOF (h^{-1}) of 8500 in comparison to 3000 for [Ru(*p*-cymene)(**79a**)]. Encouraged by this a study of different S/C ratios using [Ru(*p*-cymene)(**80**)] was carried out, and showed that even at an S/C ratio of 5000 the reaction proceeded to full conversion after 90 mins, but at an S/C ratio of 7000 the reaction stopped at 85% conversion (Table 5). The enantioselectivity was unaffected by lowering the quantity of catalyst and prolonged reaction times. The studies also showed that a wide range or aromatic ketones were reduced successfully, giving high rates/enantioselectivities with catalyst loading being as low as S/C = 1000.[17g]

Entry	S/C	Time (mins)	% conv	% ee
1	**200**	6	96	96
2	**1000**	15	97	96
3	**3000**	45	96	96
4	**4000**	70	95	96
5	**5000**	90	96	96
6	**7000**	110	85	96

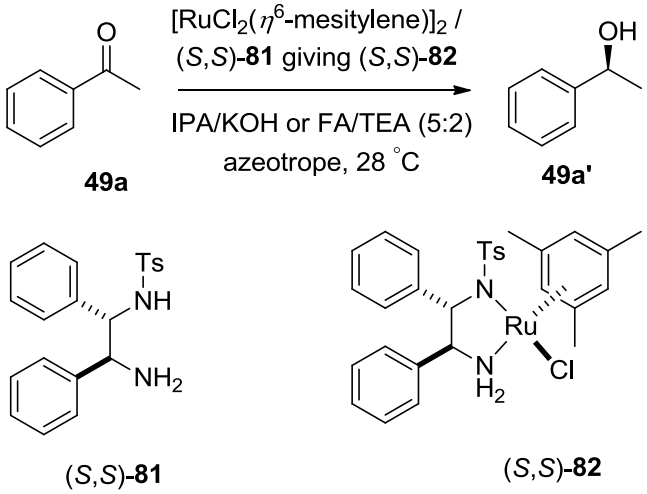
Table 5. Catalyst-loading study for the ATH of **49a** using [Ru(*p*-cymene)(**80**)] was carried out.

The highest levels of acceleration to ATH reduction reactions was obtained by beta-amino alcohols (some 70-fold over the background rate),[17h] with mono-tosylated ligands coming second (ca. 30-fold over background rate), and the others giving slightly more than 7- to 8- fold acceleration. The major drawback with the use of beta-amino alcohol ligands is its incompatibility like most other ligands with the formic acid/triethylamine

system, solving the reversibility issue which occurs in the IPA/KOH system (Section 1.4.2). Monotosylated ligands however work well with both systems.

1.4.3.2 1,2-Monotosylated ligands.

The development in the area of monotoyslated ligands out of all has been the most significant and important for ATH reactions. This area has been led by Noyori, who was the first to report the use of monoarylsulfonylated diamines, in particular **81**, as ligands in Ru(II)-catalysed transfer hydrogenation, giving excellent conversions and enantioselectivities for aromatic ketones.[17e]

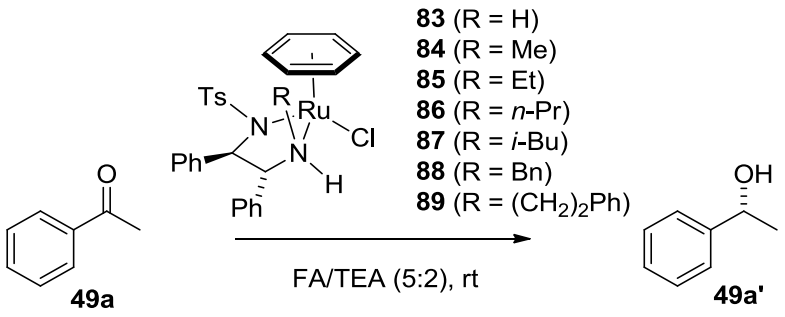


Scheme 25. The first reported use of 1,2-monotyslated diamine ligand **81** in Ru(II)-catalysed transfer hydrogenation using IPA/KOH and FA/TEA system.

Entry	Catalyst	Time (hrs)	% conv	% ee	Configuration
1[a]	**(*S*,*S*)-82**	15	95	97	*S*
2[b]	**(*S*,*S*)-82**	20	>99	98	*S*

Table 6. ATH reduction of **49a** using (*S*, *S*)-**82** in IPA/KOH and FA/TEA. [a] The reaction was carried out at room temperature using a 0.1 M solution of ketone (5.0 mmol) in IPA, KOH (0.13 mmol) with S/C = 200. [b] The reaction was carried out at 28 °C using a ketone (5.0 mmol) in FA/TEA (5:2, 2.5 cm^3) with S/C = 200.

The results show that both IPA and formic acid/triethylamine azeotrope can be utilized as hydrogen donors (Entry 1 and 2, Table 6), but the FA/TEA system using **82,**[17i] usually obtained *in situ* by heating a mixture of $[RuCl_2(\eta^6\text{-mesitylene})]_2$ with **81** in IPA at 80 °C for 20 mins under argon, afforded excellent enantioselectivities (83-99% ee) for a wide range of substrates, as the method overwhelms the energetic requirement of the reduction process (irreversible), in comparison to using IPA as the hydrogen donor where an unfavourable thermodynamic balance is expected (reversible). The activity and the ability to carry out reductions enantioselectively with such catalysts are dependent on the steric and electronic properties of the arene ligand and the chiral diamine auxiliary. The reactivity decreases in the order benzene > *p*-cymene and mesitylene > hexamethylbenzene as ligand, while mesitylene or *p*-cymene displays a better enantioselection than unsubstituted benzene.[17i] In the TsDPEN auxiliary, the presence of the NH_2 terminus was crucial as the $NHCH_3$ analogue gave much lower activity but comparable enantioselectivity; the $N(CH_3)_2$ derivative not only gave poor reactivity but also poor stereoselectivity.[17i] Wills demonstrated that instead of forming the catalyst *in situ*, reductions with isolated *N*-alkylated TsDPEN Ru(II) complexes bearing a small alkyl group proved to be highly active and enantioselective for the ATH reduction of ketones (Scheme 26).[17j]



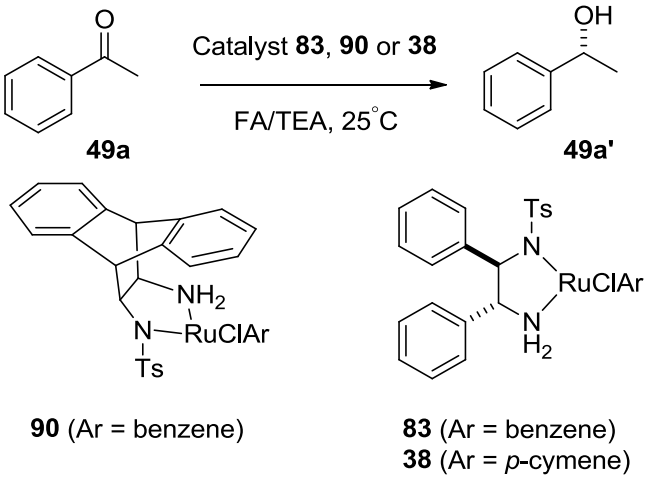
Scheme 26. ATH reduction of **49a** using Ru(II) complexes of *N*-alkylated TsDPEN ligands.

Entry	Catalyst	Time (hrs/days)	% yield	% ee	Configuration
1	**(*R*,*R*)-83**	26 hrs	99	95	*R*
2	**(*R*,*R*)-84**	11 hrs	99	96	*R*
3	**(*R*,*R*)-85**	3 days	99	96	*R*
4	**(*R*,*R*)-86**	3 days	99	96	*R*
5	**(*R*,*R*)-87**	7 days	88	98	*R*
6	**(*R*,*R*)-88**	7 days	97	95	*R*
7	**(*R*,*R*)-89**	7 days	97	96	*R*

Table 7. ATH reduction of **49a** using Ru (II) complexes of *N*-alkylated TsDPEN ligands. Reaction was carried out at room temperature using a ketone (1.0 mmol) in FA/TEA (5:2, 1.0 cm^3) with S/C = 100 and C_6D_6 (0.05 cm^3, for NMR studies).

N-Methylated complex **84** (Entry 2, Table 7) showed superior catalytic activity than Noyori's **83** (Entry 1, Table 7) and equally enantioselective. These results suggest the despite having an alkyl group on the nitrogen, the complexes are still capable of reducing ketones through the six-membered transition state established for the parent non-alkylated catalyst (Section 1.4.4). The activity however was reduced when ligands contained bulkier substituents (Entry 5-7, Table 7).[17j]

The use of a 'roofed' *cis*-1,2-diamine-Ru(II) complex **90** which is both conformationally and sterically rigid developed by Matsunaga, proved to be an excellent catalyst for the ATH of ketones, and showed higher catalytic activity than **83** and **38** (Scheme 27, Table 8), also giving higher enantioselectivity for certain bulky aromatic ketones.[17k]



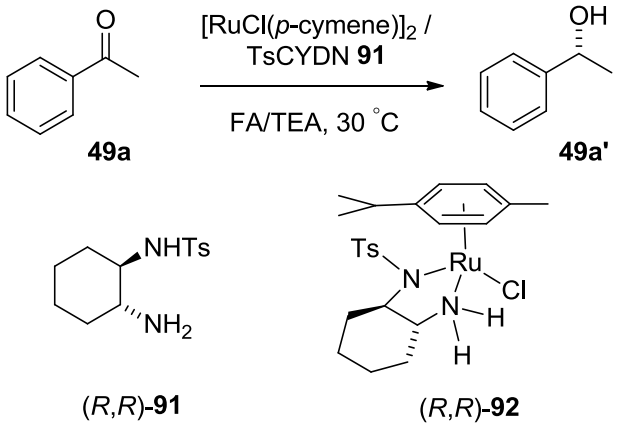
Scheme 27. ATH reduction of **49a** using catalyst **83**, **90** and **38**.

Entry	Catalyst	Time (hrs)	% yield	% ee	Configuration
1	**(*S*,*R*)-90**	15	98	93	*S*
2	**(*R*,*R*)-83**	16	98	96	*R*
3	**(*R*,*R*)-38**	20	>99	98	*R*

Table 8. ATH reduction of **49a** using catalysts **83**, **90** and **38**. Reaction was carried out at 25 °C using a ketone (2.0 mmol) in FA/TEA (5:2, 1.0 cm^3) with S/C = 200.

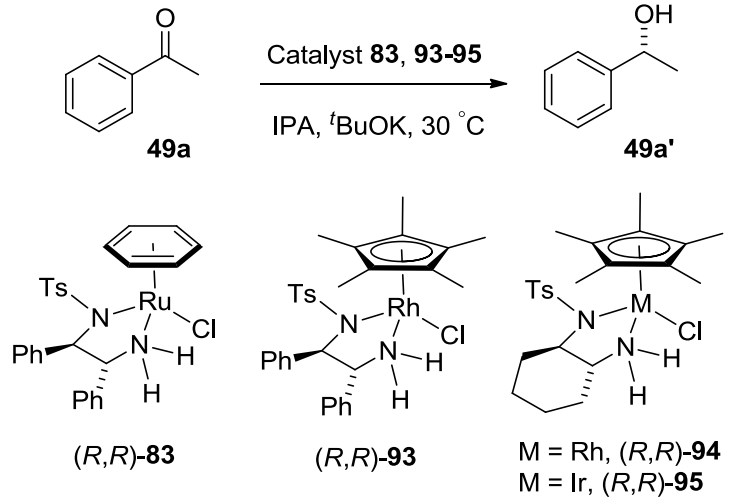
The ATH of **49a** using catalyst **90** completed the reduction process within 15 hrs, giving 98% yield and 93% ee (Entry 1, Table 8). Although **83** and **38** were slightly more enantioselective in comparison to **90**, catalyst **83** and **38** were less active, completing the reaction within 16 hrs and 20 hrs respectively.[17k]

Another example of a highly active transfer hydrogenation ligand is **91**, commonly known as TsCYDN, which was first employed in conjunction with $[RuCl(p\text{-cymene})]_2$ forming **92**, for the reduction of **49a**, giving **49a'** in >99% conversion and 94 ee (Scheme 28).



Scheme 28. Knochel demonstrated the use of **91** with [RuCl(*p*-cymene)]$_2$ for the ATH reduction of **49a**. Reaction was carried out at 30 °C in FA/TEA (5:2) with the presence of [RuCl(*p*-cymene)]$_2$ (0.5 mol%), and TsCYDN (2 mol%).

Further investigations using **91** and **81** were carried out by Ikariya, forming new chiral rhodium and iridium complexes [Cp*MCl(Tsdiamine) (M = Rh, Ir) **93-95** for the ATH reduction of aromatic ketones. The structures of the rhodium and iridium complexes formed has a structure isoelectronic with the chiral Ru complex **83** (Scheme 29).[171]



Scheme 29. ATH reduction of **49a** using new chiral rhodium and iridium complexes with chiral diamine ligands.

Entry	Catalyst	Time (hrs)	% conv	% ee	Configuration
1	**83**	12	92	94	*R*
2	**93**	12	14	90	*R*
3	**94**	12	85	97	*R*
4	**95**	12	36	96	*R*

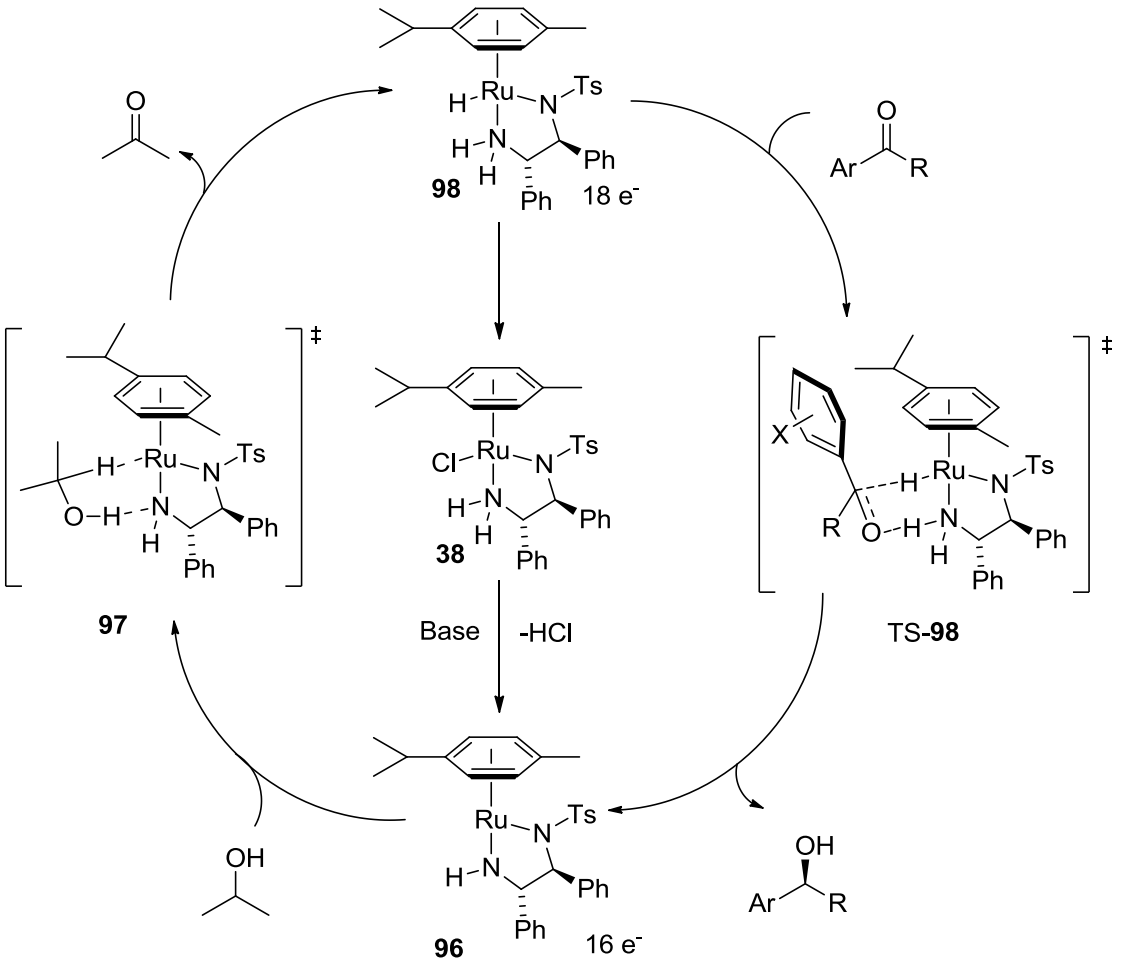
Table 9. ATH reduction of **49a** using catalyst **83**, **93-95**. Reaction was carried out at 30 °C using a 0.1 M solution of the ketone in IPA. Ketone/cat./^{t}BuOK = 200:1:1.2.

The rate and enantioselectivity of the reaction are strongly affected by the metal used and the structure of the chiral diamine ligands (Table 9). The use of TsCYDN **91** was better utilized by Rh, with complex **94** giving **49a'** in 85% conv. and 97% ee (Entry 3, Table 9) within 12 hrs in comparison to 36% conv. and 96% ee (Entry 4, Table 9) obtained within 12 hrs for Ir complex **95**. The enantioselectivity obtained with both complexes **94** and **95** were comparable, but the conversion obtained for **95** was fairly low. The use of **93**, when TsDPEN (*R*,*R*-**81**) is combined with $[Cp^*RhCl_2]_2$ for the reduction of **49a**, gave **49a'** in 14% conv. and 90% ee (Entry 2, Table 9), showing it's reactivity isn't as high as the analogous Ru complex **83** (Entry 1, Table 9), and the enantioselectivity is lower. Complexes containing diamine TsCYDN **91** might not be as reactive as its competitor diamine **81**, but the enantioselectivity obtained is higher (Entry 1, 3 and 4, Table 9).[17l]

1.4.4 Mechanistic studies.

The structural and mechanistic theory behind the successful new classes of β-aminoalcohol and monotosylated complexes synthesized by Noyori et al became targets of intense research. Noyori had proposed the metal ligand bifunctional catalytic mechanism shown in Scheme 30, which functions through a concerted transfer of a hydride and proton. It is sometimes referred to as the "outer sphere" mechanism because of the substrate having no direct contact with the metal centre. The process is initiated by the elimination of HCl via an E_{1cb} mechanism from the 18-electron "precatalyst"

complex **38**, upon treatment with an appropriate base (KOH in IPA, or triethylamine when formic acid is used as hydrogen donor). This results in the formation of the active 16 electron species **96**, which abstracts two hydrogen atoms **97** from the donor (isopropanol or formic acid) via a six-membered pericyclic transition state forming the hydride **98**.[18a] The kinetic isotope effect for the dehydrogenation of isopropanol was investigated by Casey et al,[18b] showing that hydride and proton transfer takes place simultaneously, which is in correspondence to what Noyori has shown. In a concerted process the hydride and proton is then transferred to the ketone asymmetrically via a six-membered transition state, giving the product and also regenerating the active 16-electron species. Primary and secondary amines are usually very weak acids, but after complexation with a lewis acidic metal, the NH acidity is increased allowing the NH---O=C hydrogen bond formation in the transition state TS-**98**. The rapid H/D exchange with CH_3OD also confirms the acidity of the protons prior to complexation.



Scheme 30. ATH reduction mechanism of ketones, using Noyori's catalyst **38**.

Noyori et al. isolated and characterized the three key intermediates (**38**, **96** and **98**) using X-ray crystallography. They also proved that the role of base is to only generate the active 16 electron species from **38**,[18a] as after isolation, **96** and **98** were both tested for the reduction of ketones, giving results comparable to *in situ* formed complex. This also eliminated the possibility of a direct hydrogen transfer mechanism, as this would require the participation of a ruthenium isopropoxide intermediate. Further investigations carried out by Noyori[18c] and Andersson[18d] confirmed this.

1.4.5 Origin of Enantioselection.

Noyori has demonstrated that both Ru(II) chloride **38** and Ru(II) hydride **98** exist predominantly in the diastereoisomeric form (via X-ray crystallography and molecular modelling). This preference also extends to the amino alcohol systems, which means the chiral ligand renders the metal center a single configuration. Andersson had mentioned that the generation of an enantiopure metal centre with the use of a suitable rigid ligand that disapproves other configurations of the coordinated NH group can help achieve good product enantioselectivity.[18c,18d,19a-19c]

The absolute stereochemistry for each "2H" transfer process is controlled via a six-membered transition state. The favoured approach of the substrate to the metal hydride is the conformation in which its aromatic ring is adjacent to the arene group on the metal. The aromatic group of acetophenone interacts with the η^6-arene element on the catalyst through a favourable CH/π interaction (*Si*-TS-**99**) indicated in Figure 14, and is supported by DFT calculations carried out by Noyori, which also showed that the addition of six-electron-donating alkyl groups on the η^6-arene further stabilises the TS, increasing the rate of the reaction with a drop in selectivity however (*Si*-TS-**100**).[19d-19g] This supports the observation that asymmetric reduction only takes place in high ee when aryl/alkyl ketones are used as substrates, but not with dialkyl ketones, as no CH/π interaction is present.

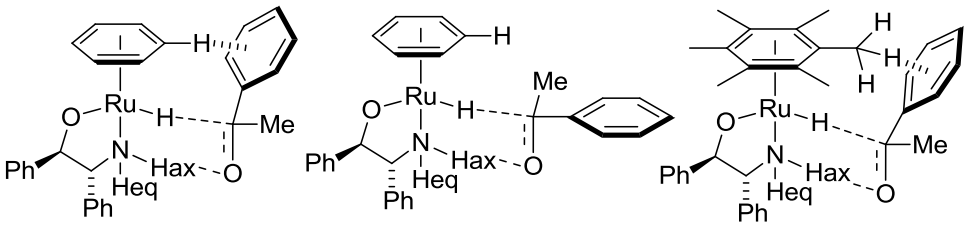
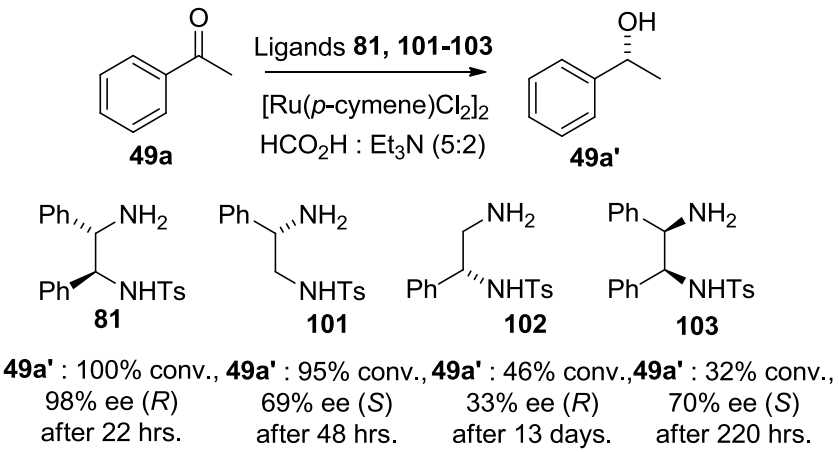


Figure 14. Stereocontrol in asymmetric transfer hydrogenation.

Noyori also investigated the effects of having electron-donating/withdrawing groups on the aryl substituent of the substrate, and its effects on the enantioselectivity. It was discovered that electron-donating substituents on the aryl group increase the enantioselectivity due to an enhanced CH accepting ability by the electron rich aromatic ring, while electron withdrawing substituents reduce the enantioselectivity.[19d, 19f, 19g]

Wills' and co-workers had investigated the *anti*-orientation, and the importance of 1,2-disubstitution pattern of phenyl groups in TsDPEN on the rate and the stereo-outcome of Ru(II) catalysed ATH reactions. It was discovered that **81** was the best ligand for Ru(II) catalysed transfer hydrogenation reduction in-terms of rate and enantioselectivity in comparison to ligands **101-103**, giving **49a'** in 100% conv., 98% ee (*R*) at 28 °C in 22 hrs. Identifying the importance of having matching stereogenic centres and *trans* orientation of the phenyl groups, providing extra element of stereo control and rate enhancement (Scheme 31).[19c]

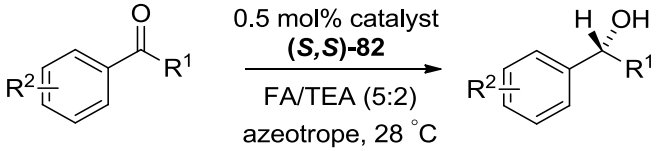


Scheme 31. ATH reduction of **49a**, using ligands **81**, **101-103** in conjunction with $[Ru(p\text{-cymene})Cl_2]_2$ (S/C = 200).

1.4.6 Range of Substrates for Asymmetric Transfer Hydrogenation.

1.4.6.1 Aryl Alkyl Ketones.

The most commonly used substrate in asymmetric transfer hydrogenation reduction are aromatic ketones, especially using monotosylated diamine or *β*-amino alcohol ligands. A variety of aromatic ketones were reduced using catalyst **(*S*,*S*)-82** (S/C = 200), in FA/TEA at 28 °C, giving the resulting secondary alcohols with excellent yields and enantioselectivities. The reason for why the reductions proceed with excellent kinetic enantioface discrimination, is due to the CH/π interaction between the Ru-arene ring and the aryl group on the ketone, along with the favourable diastereomeric transition state exerted by the monotosylated diamine ligand (Scheme 32, Table 10).[17i]



Scheme 32. A range of aryl alkyl ketones were reduced using **(*S*,*S*)-82**.

Ketone	R^2	R^1	Time (hrs)	Yield (%)	ee (%)	Config.
49a	H	CH_3	20	>99	98	*S*
49b	*m*-Cl	CH_3	21	>99	97	*S*
49c	*p*-Cl	CH_3	24	>99	95	*S*
49d	*p*-CN	CH_3	14	>99	90	*S*
49e	*m*-OCH_3	CH_3	50	>99	98	*S*
49f	*p*-OCH_3	CH_3	60	>99	97	*S*
49g	H	C_2H_5	60	96	97	*S*
49h	H	$(CH_2)_3CO_2C_2H_5$	90	99	95	*S*

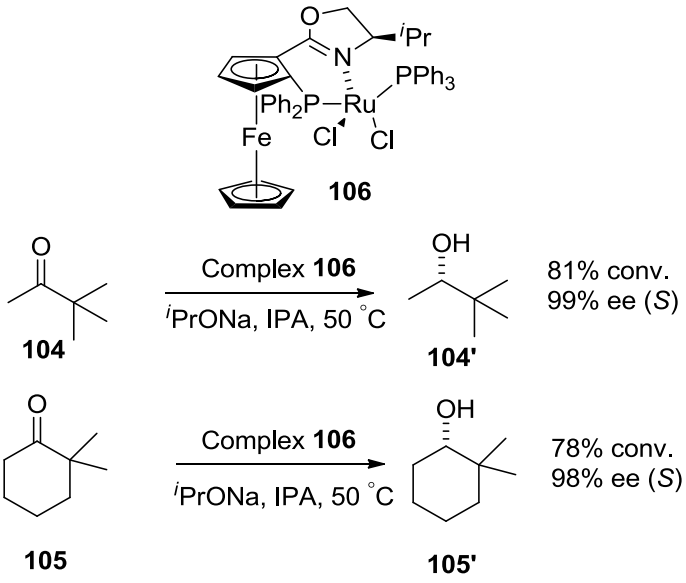
Table 10. A range of aryl alkyl ketones were reduced using **(*S*,*S*)-82**. (S/C = 200)

1.4.6.2 Dialkyl ketones.

ATH reduction of dialkyl ketones have proved to be problematic with the use of *β*-amino alcohol and monotosylated diamine ligands in conjunction with a metal precursor. This is due to the absence of the CH/π interaction, as the aromatic moiety isn't present, which earlier existed for aryl alkyl ketones. In effect, the difference in

energy between the two possible diastereomeric transition states are now narrow, resulting in poor enantioselectivity.

Wills had recently reported the reduction of cyclohexymethyl ketone using 3C "tethered" dimethyl functionalized catalyst **168** (Section 1.4.7) in FA/TEA, giving the alcohol in 100% conversion and 90% ee,[20a] which was the highest reported ee for a Ru/TsDPEN based catalyst. Other successful examples for the reduction of dialkyl ketones by ATH have been reported by Zhang[16i,16j] and Hidai.[20b] In Hidai's report, successful reduction of dialkyl ketones **104** and **105** was carried out, using ferrocene based complex [Ru(PPh_3)(osazolinyl ferrocenylphosphine)Cl_2] **106** and sodium isopropoxide in isopropanol at 50 °C. This gave **104'** in 99% ee and 81% conv., in 16 hrs, and **105'** in 98% ee and 78% conv., in 3 hrs (Scheme 33).[20b]

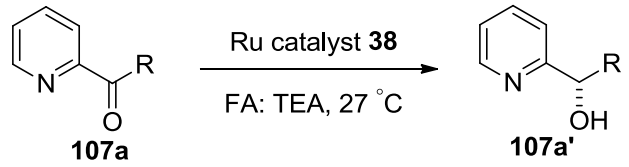


Scheme 33. ATH reduction of dialkyl ketone **104** and **105** using complex **106**.

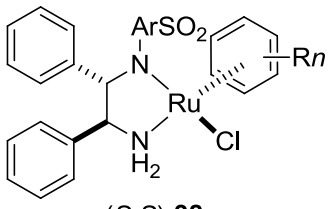
1.4.6.3 Heterocyclic ketones.

Optically active pyridyl alcohols are useful key compounds, not only as pharmaceutical intermediates, but also as useful chiral ligands and auxiliaries in asymmetric synthesis.

Ikariya reported the reduction of nitrogen-containing pyridyl ketones, using Ru(II) complex **(*S,S*)-38** in FA/TEA, giving the corresponding optically active pyridylethanols with excellent conversions and enantioselectivities. ATH reduction of 2-acetylpyridine **107a**, using Ru(II) complex **(*S,S*)-38** (S/C = 200) in a mixture of FA/TEA (acetylpyridine: FA: TEA molar ratio = 1:4.3:2.5) at 27 °C, gave (*S*)-1-(2-pyridyl)ethanol **107a'** with 97% yield and 95% ee in 12 hrs. The reduction of various derivatives **107b**-**107e**, gave good to excellent conversions (up to 100%) and ee's (up to 99.6%), except for benzoylpyridine **107e**, which gave a poor ee (9%) (Scheme 34, Table 11).[21a]



R = CH_3 (**107a**), 3-acetylpyridine (**107b**), 4-acetylpyridine (**107c**)
R = C_2H_5 (**107d**), C_6H_5 (**107e**)



(*S,S*)-**38**

a: η^6-arene = *p*-cymene; Ar = 4-$CH_3C_6H_4$

Scheme 34. ATH reduction of **107a**-**107e** using catalyst **(*S,S*)-38**. Ketone/FA/TEA molar ratio = 1:4.3:2.5.

Ketone	S/C	Temp (°C)	Time (hrs)	Yield (%)	ee (%)	Config.
107a	200	27	12	97	95	*S*
107a	200	50	12	99	91	*S*
107a[a]	200	27	24	24	89	*S*
107a	1000	27	24	91	93	*S*
107a	1000	50	24	14	78	*S*
107b	200	27	24	99	89	*S*
107c	200	27	24	99	92	*S*
107d	200	27	24	100	89	*S*
107e	200	27	24	84	9	*R*
107f[b]	200	10	24	95	86	*S*
107g[b]	200	10	24	36	85	*S*

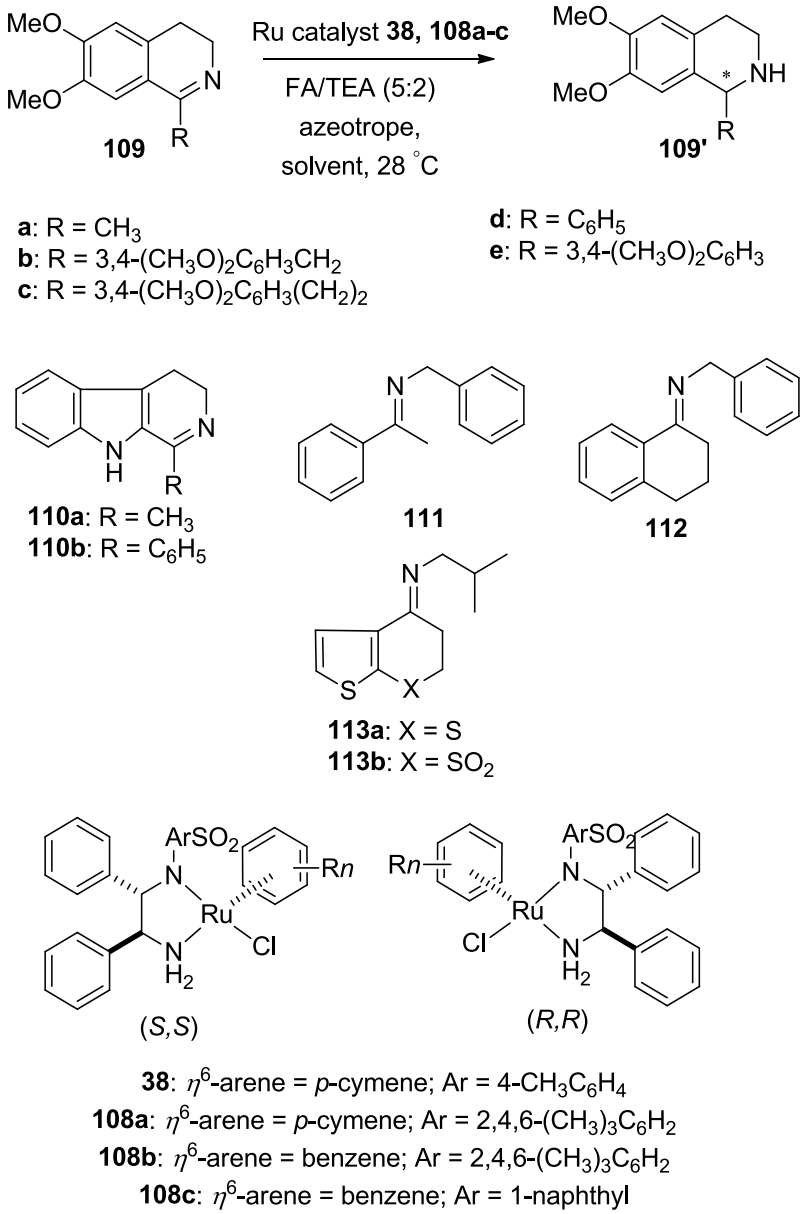
107h[c]	200	27	24	100	99.6	*S, S*

Table 11. ATH reduction of **107a-107e** using catalyst **(*S,S*)-38**. Ketone/FA/TEA molar ratio = 1:4.3:2.5. [a] Reaction in 2-propanol: (*S,S*)-Ru cat (**38**), 1.0 equiv ^{t}BuOK, ketone:Ru = 200:1, 0.1 M in 2-propanol. [b] 1.0 M in CH_2Cl_2. [c] Ketone/FA/TEA molar ratio = 1:8.6:5.0.

Asymmetric transfer hydrogenation reduction of α, β-acetylenic ketones,[21b] cyclic α, β-unsaturated ketones,[21c] and for the synthesis of styrene oxides[21d] and aziridines[21e] has also been successfully carried out.

1.4.6.4 Imines.

The synthesis of chiral amines in pharmaceuticals and agrochemical substances is highly demanding, and requires efficient catalytic asymmetric reduction of imines. Noyori reported the first highly efficient asymmetric reduction of a range of imines, using suitably designed chiral Ru(II) complexes **38, 108a-108c** in formic-acid-triethylamine mixtures under mild conditions. The reactions worked best in aprotic solvents including MeCN, DMF, DMSO and CH_2Cl_2, but not in ethereal or alcoholic media, and neat FA/TEA (slow reaction rate). The structure of the Ar group and the substitution pattern of η^6-arene ligand on the Ru complex, were fine-tuned depending on the substrates used. The ATH reduction of imine **109a** was most successful, using (*S, S*)-**38** (S/C = 200) in FA/TEA (5:2) and acetonitrile at 28 °C, giving salsolidine **109a'** (*R*) in 95% ee and >99% yield in 3 hrs. Various other cyclic imine derivatives **109b-109e** were reduced, giving excellent conversions (up to >99%) and enantioselectivities (up to 95%). This method was further applied to the synthesis of indoles **110a-110b**, giving good yields (up to 89%) and excellent enantioselectivities (up to 97%), and the reduction of acyclic imines **111-113**, which gave good conversions (up to 90%) but were less stereoselective (ee's of up to 89%) (Scheme 35, Table 12).[22]



Scheme 35. ATH reduction of **109a-109e** and **110-113**, using catalyst **38, 108a-108c**.

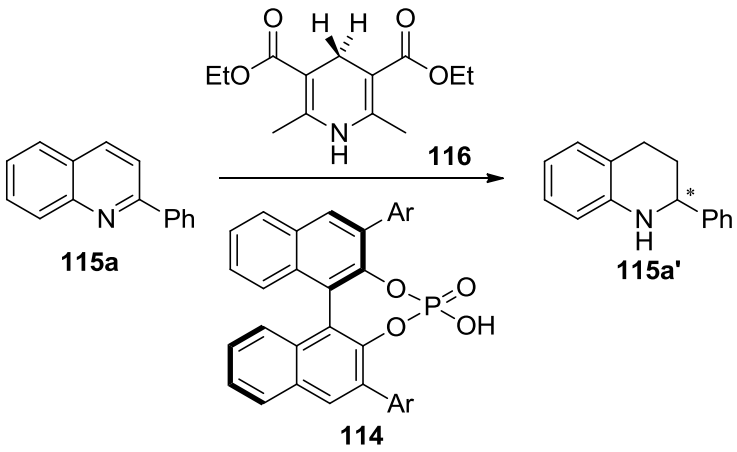
Imine	Catalyst	S/C	Solvent	Time (hrs)	Yield (%)	ee (%)	Config.
109a	(*S*,*S*)-**38**	200	CH_3CN	3	>99	95	*R*
109a	(*S*,*S*)-**38**	1000	CH_3CN	12	97	94	*R*
109b	(*R*,*R*)-**108a**	200	$(CH_3)_2NCHO$	7	90	95	*S*
109c	(*R*,*R*)-**108a**	200	CH_2Cl_2	12	99	92	*S*
109d	(*S*,*S*)-**108c**	200	CH_2Cl_2	8	99	84	*R*
109e	(*R*,*R*)-**108c**	100	CH_2Cl_2	12	>99	84	*S*
110a	(*S*,*S*)-**38**	200	$(CH_3)_2NCHO$	5	86	97	*R*
110a	(*S*,*S*)-**38**	1000	$(CH_3)_2NCHO$	12	89	93	*R*
110b	(*S*,*S*)-**38**	200	$(CH_3)_2NCHO$	5	83	96	*R*
111	(*S*,*S*)-**108b**	200	CH_2Cl_2	36	72	77	*S*
112	(*S*,*S*)-**108c**	100	CH_2Cl_2	6	90	89	*S*
113a	(*S*,*S*)-**108c**	100	CH_3CN	12	82	85	*S*
113b	(*S*,*S*)-**108c**	100	CH_3CN	5	84	88	*S*

Table 12. ATH reduction of **109a-109e** and **110-113**, using catalyst **38, 108a-108c**.

1.4.6.5 Quinolines.

Asymmetric hydrogenation of quinolines, giving 1, 2, 3, 4-tetrahydroquinolines has been described earlier in Section 1.3.3.6, along with its synthetic importance. The first example of a metal-free *transfer hydrogenation* reduction of quinolines was reported in 2006.[23a] Rueping used his expertise and extended his research from the already developed enantioselective Brønsted acid catalysed hydrogenation of imines,[23b,23c] in to the enantioselective reduction of quinolines.

Using Brønsted acid **114**, 2-phenylquinoline **115a** as a test substrate for reduction and dihyropyridine **116** as the source of hydride, the structure of catalyst **114** was studied (Scheme 36, Table 13).

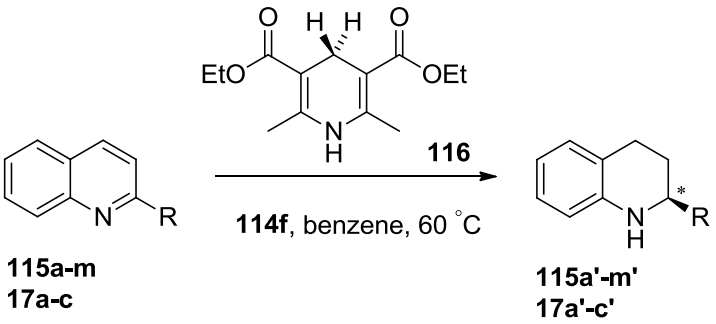


Scheme 36. Reduction of 2-phenylquinoline, using **114** and **116**.

Entry	Cat.	Ar	ee (%)
1	**114a**	Phenyl	5
2	**114b**	4-biphenyl	35
3	**114c**	1-naphthyl	84
4	**114d**	2-naphthyl	26
5	**114e**	3,5-(CF_3)-C_6H_3	72
6	**114f**	9-phenanthryl	97

Table 13. Studying acid **114** for the cascade transfer hydrogenation of 2-phenylquinoline. Reaction was carried out in benzene at 60 °C, with **115a**, **116** (2.4 equiv) and **114** (5 mol %).

The results showed that sterically congested Brønsted acids were best catalysts for hydride transfer and gave good to excellent enantioselectivities, with the highest selectivity being obtained using **114f,** providing 2-phenyltetrahydroquinoline **115a'** in 97% ee. Investigation on various solvents was also carried out with nonpolar solvents (chlorinated: CH_2Cl_2, $CHCl_3$, CCl_4 and aromatic: benzene, toluene) proving to be crucial for high asymmetric induction. Benzene emerged to be the best solvent in this system giving the highest enantioselectivity.[23a]



Scheme 37. Brønsted acid catalysed cascade transfer hydrogenation of 2-substitued quinolines under optimized conditions.

Quinoline	R	Time (hrs)	Yield (%)	ee (%)
115a	phenyl	12	92	97
115b	2-fluorophenyl	30	93	98
115c	2-methylphenyl	48	54	91
115d	2,4-dimethylphenyl	60	65	97
115e	2-naphthyl	12	93	>99
115f	3-bromophenyl	18	92	98
115g	4-(CF_3)-C_6H_3	30	91	>99
115h	1,1'-biphenyl-4-yl	12	91	>99
115i	4-methoxyphenyl	12	90	98
115j	2-furyl	12	93	91
115k	chloromethyl	12	91	88
115l	*n*-butyl	12	91	87

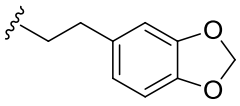
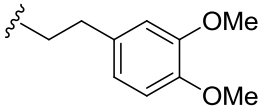
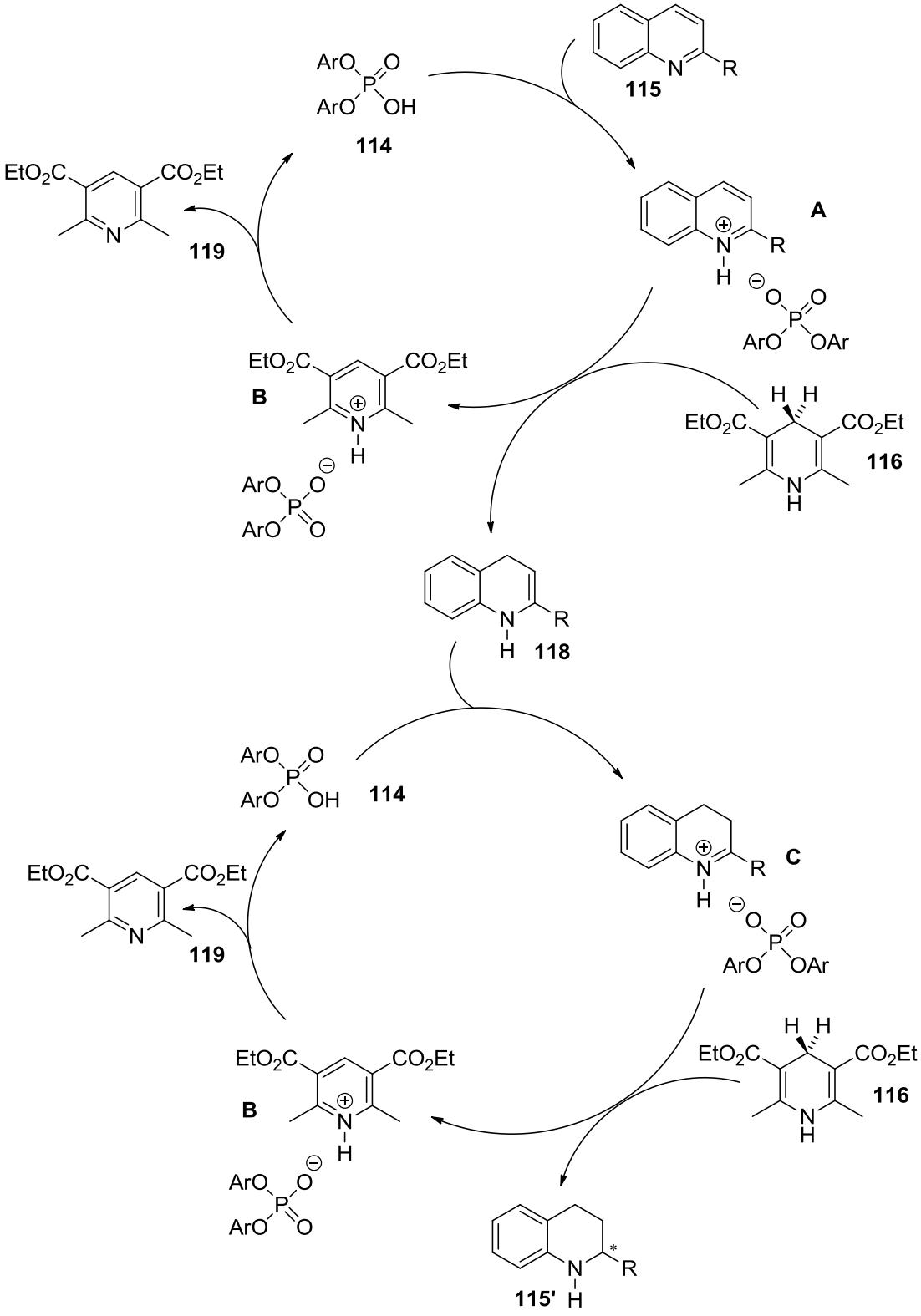
115m	*n*-pentyl	12	88	90
117a	2-phenylethyl	12	90	90
117b		12	94	91
117c		12	95	90

Table 14. Transfer hydrogenation reduction of 2-substitued quinolines. Reaction was carried out in benzene at 60 °C with **115a-m** and **117a-c**, **116** (2.4 equiv) and catalyst **114f** (2 mol%).

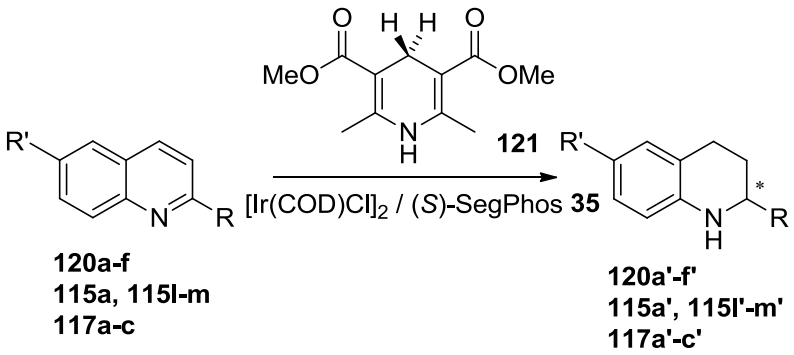
Bronsted acid catalysed cascade transfer hydrogenation reduction using the optimized conditions were carried out on a series of 2-substituted quinolines (Scheme 37, Table 14). The results showed that high enantioselectivites (up to >99%) and good yields (up to 95%) of several tetrahydroquinolines, with aromatic, heteroaromatic residues as well as aliphatic substituents were obtained. The system was also compatible with halogenated aromatic and aliphatic residues.[23a]

The proposed mechanism for this process: initiation with Brønsted acid catalyst **114** protonating quinoline **115**, forming the active iminium ion **A**. Subsequent transfer of hydride from **116**, gives the enamine **118** and pyridinium salt **B**. Brønsted acid **114** is regenerated after proton transfer from **B**, forming Hantzsch pyridine **119**. The desired tetrahydroquinoline is formed **115'**, after the reaction of enamine **118** in a second cycle with Brønsted acid **114**, forming iminium **C** which is subjected to hydride transfer from dihydropyridine **116** (Scheme 38).[23a]



Scheme 38. Proposed mechanism for the Brønsted acid catalysed cascade transfer hydrogenation.

The use of Hantzsch esters was further applied by Zhou in his system.[23d] In 2007, Zhou reported the first metal catalysed asymmetric transfer hydrogenation of quinolines **120a-f**, **115a**, **115l-m**, **117a-c**, using $[Ir(COD)Cl]_2$/(*S*)-SegPhos **35**/I_2 and a Hantzsch ester **121** (Scheme 39).



Scheme 39. Ir-catalysed asymmetric transfer hydrogenation of quinolines.

The optimized conditions for this system were obtained from studying the effects of solvents, different ligands, and different sizes of Hantzsch esters. In the study of solvent effects, solvents including THF, DME, toluene, DCM and dioxane were used. The two solvents that gave great results were toluene and dioxane, with the highest reactivity given by dioxane and highest enantioselectivity by toluene. Some commercially available ligands (Figure 15) were screened including (*S*)-MeO-BiPhep **31**, (*S*)-SegPhos **35**, (*S*)-SynPhos **122**, (*R*, *R*)-Me-DuPhos **123**, (*R*)-Cl-MeOBiPhep **124** and (*S*)-BINAP **125**, with the best result given by (*S*)-SegPhos **35**.[23d]

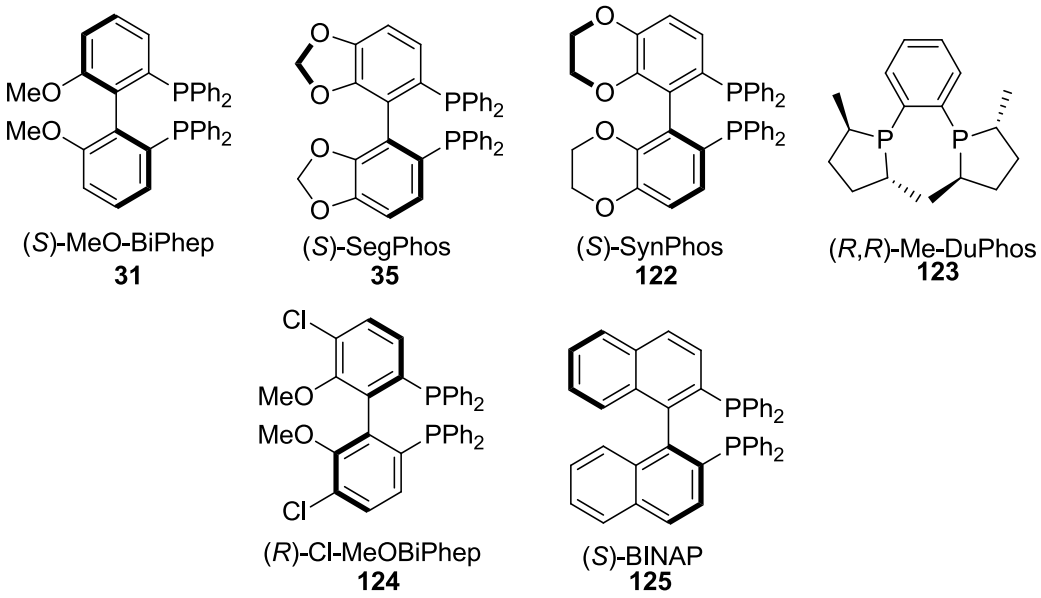
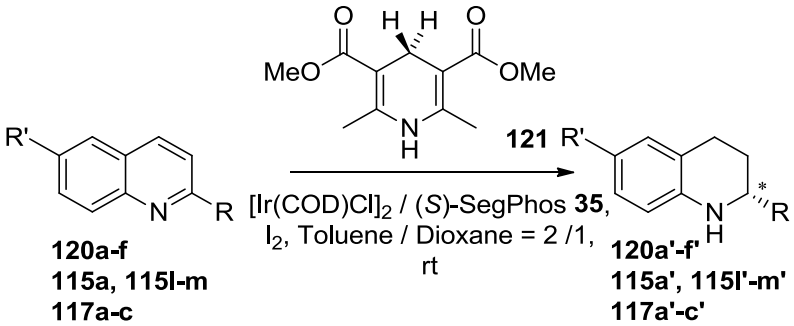


Figure 15. Commercially available chiral ligands screened.

In the investigation of different Hantzsch ester sizes, dimethyl Hantzsch **121** ester out of diethyl-, di-^{i}propyl- and di-^{t}butyl gave the highest rate and enantioselectivity. The ATH reduction of 2-methylquinoline **120a** was then carried out using $[Ir(CODCl]_2$ / (*S*)-SegPhos **35**, dimethyl Hantzsch ester **121**, 2/1 toluene/dioxane in presence of iodine at rt (Scheme 40), and the best overall result was obtained, giving 2-methyl-1,2,3,4-tetrahydroquinoline **120a'** in 86% yield and 87% ee (Entry 1, Table 15). Once the optimal conditions were established, various quinolines were reduced (Entry 2-12, Table 15).[23d]



Scheme 40. Ir-catalysed asymmetric transfer hydrogenation of quinolines, using optimal conditions.

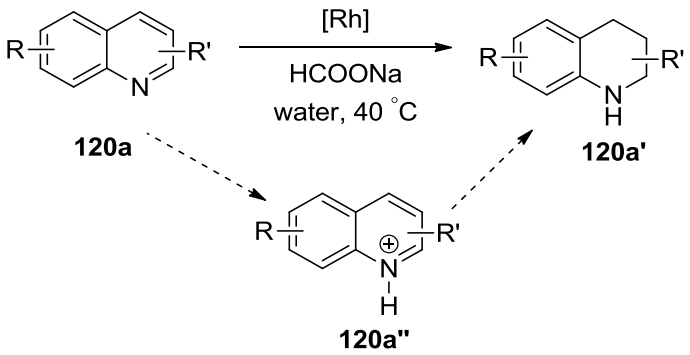
Entry	R'/R	Yield (%)	Time (hrs)	ee (%)	Config.
1	H/Me	86 **(120a)**	42	87	(*S*)
2	H/Et	92 **(120b)**	42	87	(*S*)
3	H/*n*-Bu	98 **(115l)**	42	81	(*S*)
4	H/*n*-Pentyl	94 **(115m)**	45	68	(*S*)
5	F/Me	90 **(120c)**	45	86	(*S*)
6	Me/Me	82 **(120d)**	56	86	(*S*)
7	MeO/Me	43 **(120e)**	74	81	(*S*)
8	H/Phenethyl	88 **(117a)**	45	87	(*S*)
9	H/3,4-Methylenedioxyphenethyl	87 **(117b)**	46	87	(*S*)
10	H/3,4-$(MeO)_2C_6H_3(CH_2)_2$-	92 **(117c)**	46	88	(*S*)
11	H/$Ph_2C(OH)CH_2$-	76 **(120f)**	79	78	(*R*)
12	H/Ph	90 **(115a)**	69	10	(*R*)

Table 15. Ir-catalysed asymmetric transfer hydrogenation of quinolines, using optimal conditions. Reaction was carried out at rt using quinoline (0.25 mmol), $[Ir(COD)Cl]_2$ (1 mol%), ligand (2.2 mol%), I_2 (5 mol%), solvent (2.5 cm^3) and Hantzsch ester (2.0 equiv)

The results showed that for 2-alkyl substituted quinolines, good yields (up to 98% yield), and enantioselectivities (up to 87%) were obtained, with the enantioselectivity decreasing when the length of the side chain is increased (Entry 1-4, Table 15). The reaction time had increased when having substituents at the 6-position (Entry 5-7, Table 15), with low conversion also being obtained if the group at the 6-position is electron donating. 2-(2-Arylethyl)-substituted quinolines (Entry 8-11, Table 15) were reduced in good yields (up to 92% yield) and enantioselectivities (up to 88% ee), and the system can also withstand substrates that have a hydroxyl group present (Entry 11, Table 15). Good yield was obtained with 2-aryl substituted quinoline, but the enantioselectivity was poor (10% ee) (Entry 12, Table 15).[23d]

ATH reduction using Hantzsch esters as the source of hydrogen have given excellent results with both metal-free and Ir/diphosphine-catalysed methods. Xiao et al. in 2010

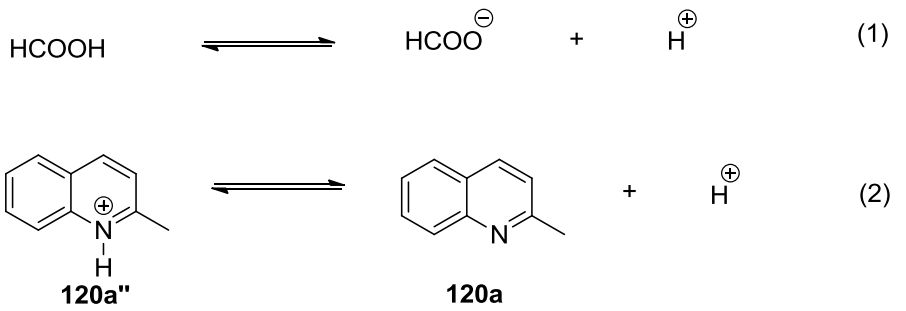
reported the first ATH of quinolines in aqueous solution using a metal catalyst (Scheme 41),[23e] with the reaction being carried out in air, giving excellent enantioselectivities for a wide range of substrates. The use of water does not only offer new reactivity and selectivity patterns but also advantageous economic and ecological gains.[23e]



Scheme 41. ATH of quinolines in water, and showing the possible reaction intermediate.

Previously, ATH reduction of ketones and imines was studied in neat water,[23e] using TsDPEN **81** with Ir [$(Cp^*IrCl_2)_2$], Rh [$(Cp^*RhCl_2)_2$] and Ru [$\{RuCl_2(p\text{-cymene})\}_2$] metals, from which Rh-TsDPEN catalyst showed highest reactivity and selectivity.[23f] Due to this, initial studies for the reduction of 2-methylquinoline **120a** were carried out using presynthesized Rh-TsDPEN catalyst[23g] with HCOONa in water. This particular method gave a very poor conversion but excellent enantioselectivity. Xiao and co-workers had previously studied the ATH of ketones in water, and had established that the rate of reaction was dependant on the pH of the solution.[23f,23h] Taking this in to account, the pH effect of solution for the reduction of quinolines was examined, by monitoring the conversion at initial pH values of solution, from 3 up to 8 (via altering HCOOH/HCOONa ratio). The results showed that the highest conversion was obtained at initial pH of 5, which gets very close to the pK_a of protonated quinoline **120a''** (5.4), supporting the ionic mechanism pathway that has been previously suggested for the

reduction of quinolines in its protonated form. [9g, 17j, 23a, 23i-l] This also explains why such a low conversion was obtained in the earlier studies as the pH of the solution at the start of the reaction was 8 (Scheme 41).



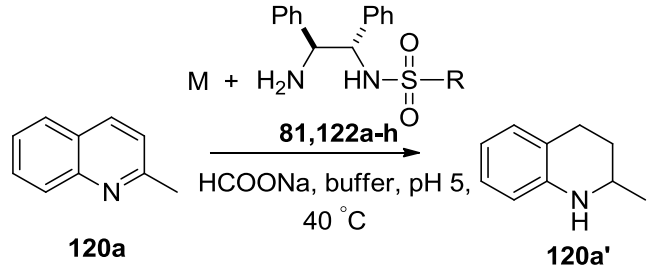
Scheme 42. The pH effect can be expressed with the two opposing equilibria shown: (1) and (2).

The concentration of **120a''** decreases at high pH values (pH > 5.4), and at low pH values (pH < 3.6) the concentration of formate becomes low. So having a pH between 3.6 and 5.4 would be ideal for obtaining high reaction rates as it would provide a high concentration of both reactants (Scheme 42).[23e]

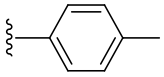
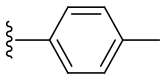
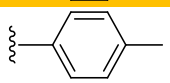
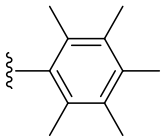
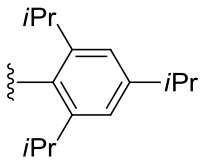
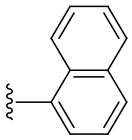
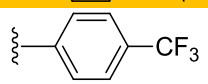
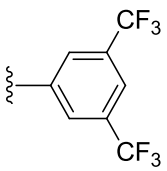
The use of a buffered solution had resolved this issue, as it was able to maintain the pH of solution and avoid pH fluctuation. The buffer capacity of HCOOH/HCOONa pair with a pK_a value of 3.6 was not sufficient, but the use of HOAc/NaOAc, having maximum buffer capacity of pH 5 proved to be ideal in this ATH system. ATH of **120a** in 2 M HOAc/NaOAc buffer solution gave the resulting 1,2,3,4-tetrahydroquinoline **120a'** with 95% conversion and 96% ee in 3 hrs.[23e]

In the attempt to further improve the ATH efficiency, various metal precursors (Entry 1-3, Table 16) and ligands (Entry 4-12, Table 16) were tested for the reduction of **120a** using the optimized conditions (Scheme 43). The metal precursor $[(Cp^*RhCl_2)_2]$, in comparison to the isoelectronic $[\{RuCl_2(p\text{-cymene})\}_2]$ and $[(Cp^*IrCl_2)_2]$ (Entry 1-3,

Table 16), gave the best result with TsDPEN **81** as the ligand. Using [(Cp*RhCl$_2$)$_2$], various ligands were tested (Entry 4-12, Table 16) from which **122d** gave the best reactivity and selectivity.[23e]



Scheme 43. Reduction of **120a** using different metal precursors and various ligands.

Entry	M	Ligand	R	Conv. (%)	ee (%)
1	[{RuCl$_2$(*p*-cymene)}$_2$]	**81**		32	90
2	[(Cp*IrCl$_2$)$_2$]	**81**		88	11
3	[(Cp*RhCl$_2$)$_2$]	**81**		95	96
4	[(Cp*RhCl$_2$)$_2$]	**81**		49	96
5	[(Cp*RhCl$_2$)$_2$]	**122a**		13	83
6	[(Cp*RhCl$_2$)$_2$]	**122b**		12	74
7	[(Cp*RhCl$_2$)$_2$]	**122c**		34	94
8	[(Cp*RhCl$_2$)$_2$]	**122d**		55	97
9	[(Cp*RhCl$_2$)$_2$]	**122e**		48	96
10	[(Cp*RhCl$_2$)$_2$]	**122f**		31	94

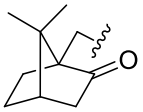
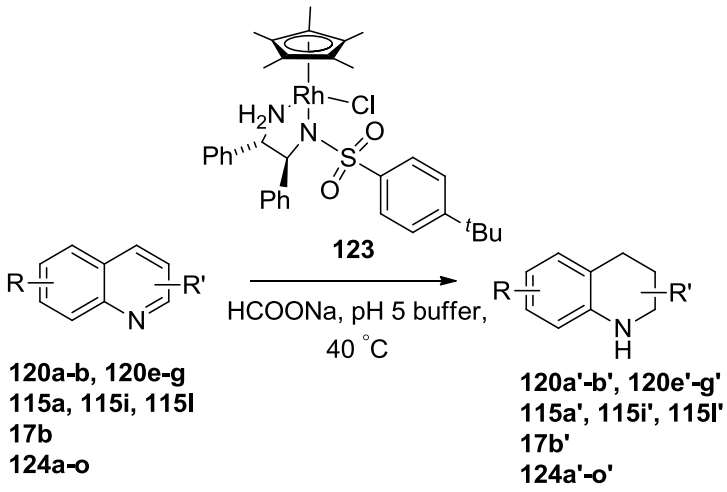
11	[(Cp*RhCl$_2$)$_2$]	**122g**		39	90
12	[(Cp*RhCl$_2$)$_2$]	**122h**	CH_3	27	94

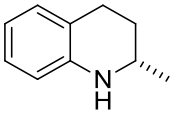
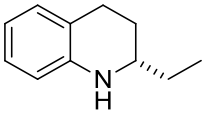
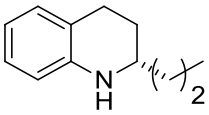
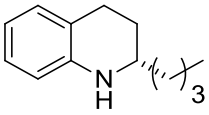
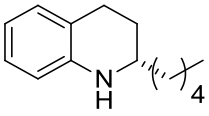
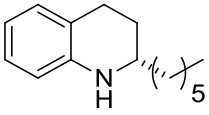
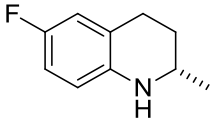
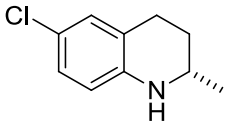
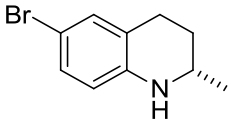
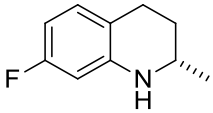
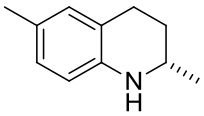
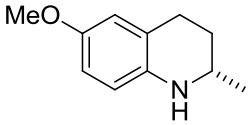
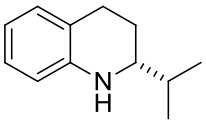
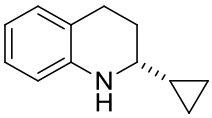
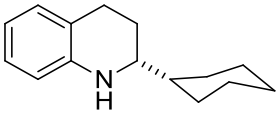
Table 16. Reduction of **120a** using different metal precursors and various ligands. Reaction was carried out at 40 °C, using quinoline (0.5 mmol), metal precursor (2.5 μmol), ligand (6 μmol), HCOONa (5 mmol) and 2 M HOAc/NaOAc buffer solution (5 cm^3). Reaction time was 12 hrs for entries 1-3 and 0.5 hrs for entries 4-12.

As a result (Entry 8, Table 16), complex **123** (Scheme 44) was prepared using ligand **122d** and [(Cp*RhCl$_2$)$_2$], which was selected as the catalyst for the ATH reduction of a series of quinolines (Entry 1-25, Table 17) in an aqueous formate solution buffered to pH 5 with HOAc/NaOAc.[23e]

Excellent enantioselectivities and yields were observed for a range of substrates, with the alkyl chain length in the 2-position, and substituents in 6- or 7- position having little effect on the enantioselectivity. The yield was however lowered with having electron-rich substituents at the 6-position. 2-Phenyl-substituted quinolines were better reduced at a lowered pH value of 4, with the catalyst formed when ligand **122f** was combined with [(Cp*RhCl$_2$)$_2$].[23e]



Scheme 44. ATH reduction of a range of quinolines using catalyst **123**.

Entry	Product	Product	Yield (%)	ee (%)
1	**120a'**		96	97
2	**120b'**		95	96
3	**124a'**		93	97
4	**115l'**		94	97
5	**115m'**		95	97
6	**124b'**		92	97
7	**120e'**		96	96
8	**124c'**		95	96
9	**124d'**		96	95
10	**124e'**		97	96
11	**120f'**		91	96
12	**120g'**		90	98
13	**124f'**		86	91
14	**124g'**		88	98
15[a]	**124h'**		87	96

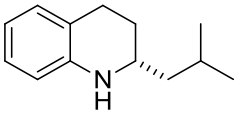
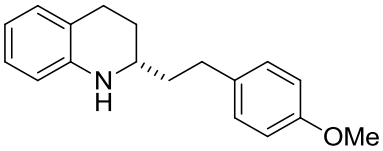
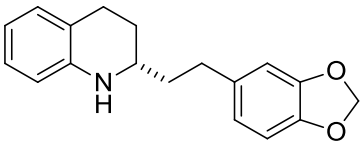
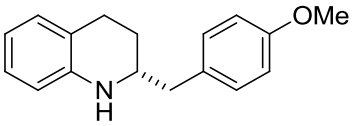
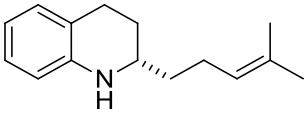
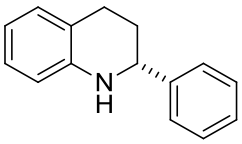
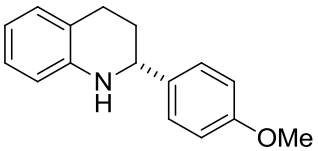
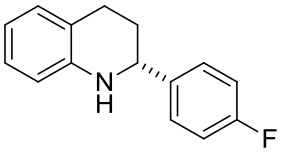
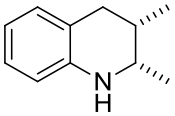
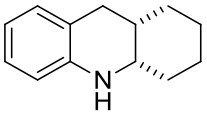
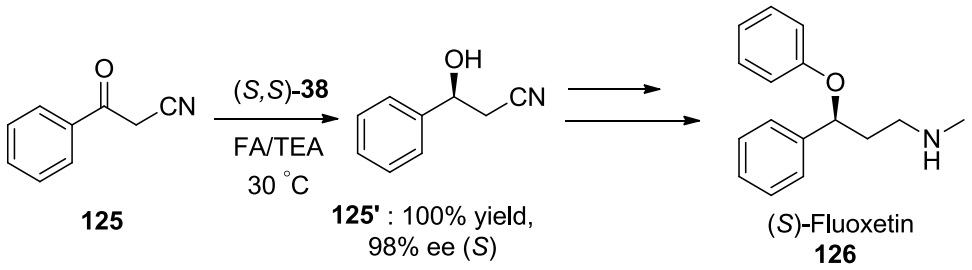
16	**124i'**		97	97
17	**124j'**		84	97
18	**117b'**		85	97
19	**124k'**		80	96
20	**124l'**		90	97
21[b]	**115a'**		96	90
22[b]	**115i'**		95	90
23[b]	**124m'**		93	89
24[a]	**124n'**		89	92 (4 : 1)[c]
25	**124o'**		95	86 (99 : 1)[c]

Table 17. ATH reduction of a range of quinolines using catalyst **123**. Reaction was carried out at 40 °C, using quinoline (0.5 mmol), **123** (5 μmol), HCOONa (5 mmol) and buffer solution (5 cm^3). Reaction time was between 6-24 hrs. [a] 2 mol% of **123** used. [b] ligand **122f** used at pH 4 in 2 M HOAc/NaOAc buffer solution (5 cm^3) with EtOAc (0.3 cm^3). [c] diastereoselectivity in brackets.

1.4.6.6 Synthesis of Biologically Active Compounds.

1.4.6.6.1 (*S*)-Fluoxetin.

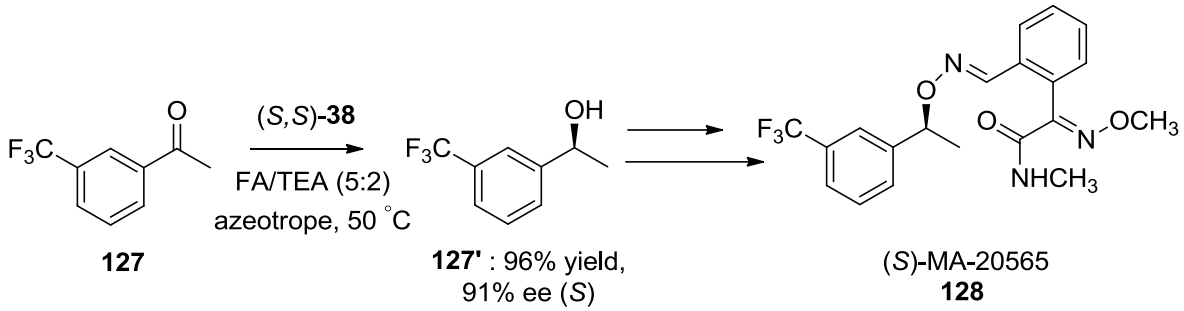
(*S*)-Fluoxetin **126** is an anti-depressant used for the treatment of clinical depression. A practical method was reported by Ikariya using ATH for the synthesis of (*S*)-fluoxetin **126**. ATH reduction of 2-cyanoacetophenone **125** using catalyst (*S*,*S*)-**38** in formic acid/triethylamine at 30 °C, gave the key intermediate **125'** for the formation of (*S*)-fluoxetin **126** in 100% yield and 98% ee in 24 hrs (Scheme 45).[24a]



Scheme 45. ATH reduction of **125** in FA/TEA (3.1:2.6), using catalyst (*S*,*S*)-**38** (S/C = 1000) gave the key product **125'**, for the synthesis of (*S*)-fluoxetin **126**.

1.4.6.6.2 (*S*)-MA-20565.

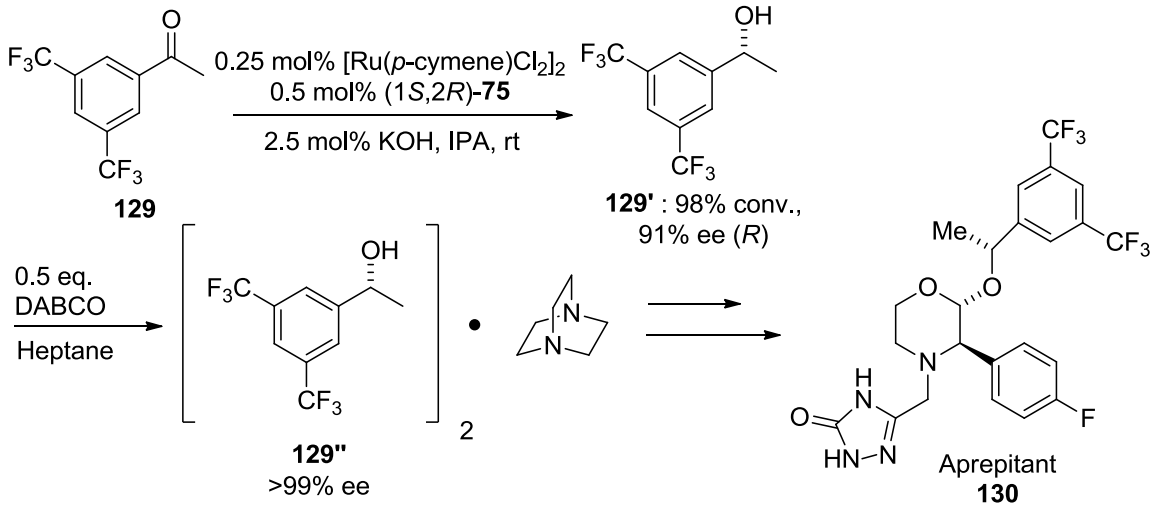
(*S*)-MA-20565 **128** is a wide-spectrum agricultural fungicide, and the formation of the key intermediate step can be carried out using ATH as reported by Tanaka et al. The reduction of 1-(3-(trifluoromethyl)phenyl)ethanone **127**, using (*S*,*S*)-**38** (S/C = 5000) in FA/TEA (5:2) azeotrope at 50 °C, gave the key intermediate **127'** in 96% conv., and 91% ee after 30 hrs (Scheme 46).[24b]



Scheme 46. ATH reduction of **127** in FA/TEA (5:2), using catalyst (*S*,*S*)-**38** (S/C = 5000) gave the key product **127'**, for the synthesis of (*S*)-MA-20565 **128**.

1.4.6.6.3 Aprepitant.

Aprepitant **130** is an antimetic compound that belongs to a class of drugs called substance P antagonists. It mediates its effect by blocking the neurokinin 1 (NK_1) receptor, and is used for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. The key intermediate for this drug **129'** can be obtained by ATH. The reduction of 1-(3,5-bis(trifluoromethyl)phenyl)ethanone **129**, using Ru(II) complex of (1*S*,2*R*)-*cis*-aminoindanol **75** combined with $[Ru(p\text{-cymene})Cl_2]_2$ (S/C = 200) and KOH in IPA at rt, gave the key intermediate **129'** of Aprepitant **130** in 98% conv., and 91% ee (*R*) after 4 hrs. The enantioselectivity of the product can be further enhanced by isolation of the alcohol **129'** as its DABCO complex **129''**, giving >99% ee (Scheme 47).[24c]



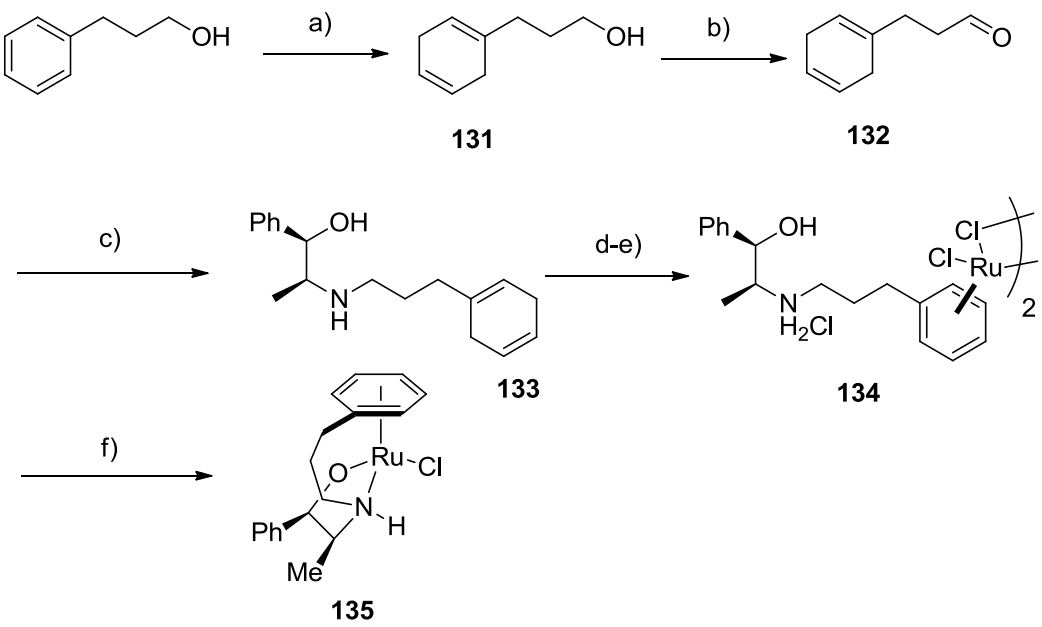
Scheme 47. ATH of **129** using Ru(II) complex of **75**, giving the key intermediate **129'** followed by **129''** prior to isolation as a DABCO complex.

ATH has also been applied for the synthesis of an intermediate of L-699,392 (LTD_4 antagonist)[17i] and can also be used to reduce sulphur containing ketones in order to prepare the intermediate for MK-0417.[17i]

1.4.7 Asymmetric transfer hydrogenation using ruthenium(II) "tethered" catalysts.

In recent years, successful structural modifications have been carried out on Noyori's catalysts, based on Ru(II) complexes of amino alcohols and monotosylated diamines such as complex **99** and **38** respectively. A new class of "tethered" Ru(II) catalysts was developed by Wills and co-workers in 2004, where the chiral amino alcohol or monosulfonylated diamine is covalently bound to the η^6-arene group through a hydrocarbon bridge. The tether link allows "locking" of the otherwise freely rotating aryl group, and permits control over the spatial positions of the substituents on this ring. Furthermore, the stability of the catalyst is increased due to attachment of the ligand to the metal at three points, reducing ligand dissociation from the metal centre.

The synthesis of "tethered" amino alcohol catalyst **135** has been outlined in Scheme 48. The formation of chloro-bridged η^6-arene ruthenium(II) complex **134**, from the reaction of **133**.HCl with $RuCl_3$ under reflux in ethanol was the major step towards the formation of **135**. The protonation of amine group in **133** is essential to form dimer **134**, as the attempted reaction with free amine resulted in formation of complex product mixtures, possibly due to the chelation of Ru(III) by the free amine outpacing arene oxidation.[25a]

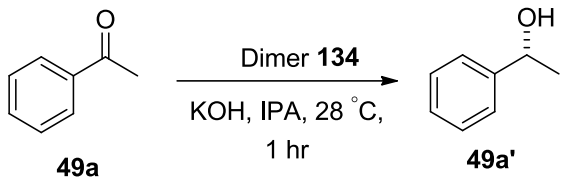


a) Na, NH_3, EtOH, -78 °C, 3 hrs; (b) $(ClCO)_2$ (1.2 eq), DMSO (2.5 eq), Et_3N (5.5 eq), DCM, -78 °C, 80 mins; c) i) 4Å molecular sieves, L-(-)-norephedrine (1 eq), DCM, rt, o/n, ii) $NaBH_4$ (3 eq), MeOH, rt, o/n; d) HCl, Et_2O, rt; e) $RuCl_3$ hydrate, EtOH, reflux, 21 hrs (two steps).

Scheme 48. Synthetic route for the formation of dimer **134**, forming **135** *in situ* under the ATH reduction conditions.

Although Wills and co-workers were not able to isolate **135** from the treatment of **134** with base, **135** however did form *in situ* during reduction of acetophenone **49a** by dimer **134** in IPA with KOH, giving the resulting alcohol in 96% yield and 66% ee after 1 hr (Scheme 49). The yield and ee obtained in this reaction is an improvement to what has

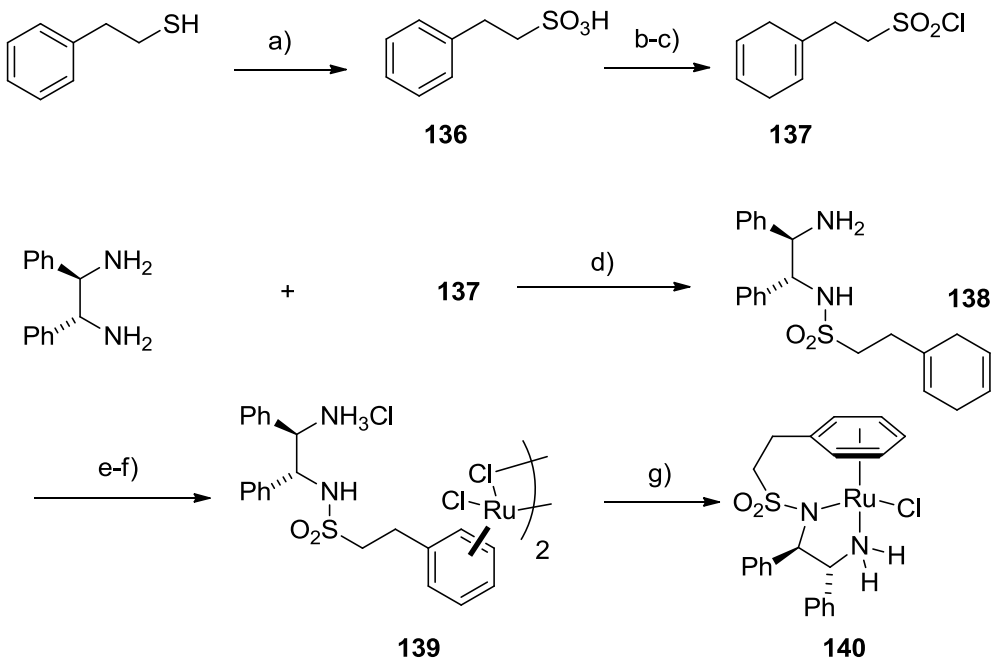
been obtained using analogous non-tethered catalyst derived from the combination of (1*R*,2*S*)-ephedrine and $[Ru(benzene)Cl_2]_2$ (86% yield, 58% ee). Dimer **134** failed to react in formic acid/triethylamine (5:2) azeotrope mixture, like other amino alcohol based catalysts previously mentioned (Section 1.4.3.1).[25a]



Dimer **134**: 96% yield, 66% ee (*R*)
Non-tethered analogue: 86% yield, 58% ee (*R*)

Scheme 49. ATH reduction of **49a** using dimer **134**, and its non-tethered analogue.

As well as amino alcohol, monosulfonylated diamine "tethered" catalysts such as **140** can also be synthesized. But unlike **135**, monosulfonylated diamine catalyst **140** can be isolated from the reaction of dimer **139**, with Et_3N, in refluxing IPA for 1 hr. The X-ray crystal structure of **140** confirmed the presence of the "tether" link, and showed that the ligand coordinates to the metal centre in a similar manner to the non-tethered analogue (Complex formed from the combination of $[Ru(benzene)Cl_2]_2$ with TsDPEN) (Scheme 50).[25a]



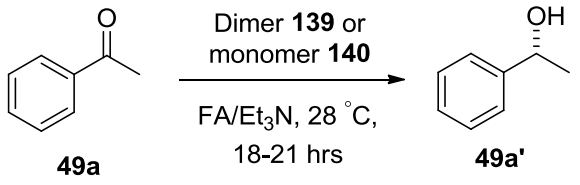
a) CH_3CO_3H (36-40% in acetic acid) (3 eq), DCM, rt, 2 hrs; b) Na, NH_3, EtOH, -78 °C, 3 hrs; c) $SOCl_2$ (20 eq), DMF (2 eq), DCM, 35 °C, 16 hrs; d) Et_3N (2 eq), DCM, rt, o/n; e) HCl, Et_2O, rt; f) $RuCl_3$ hydrate, EtOH, reflux, 21 hrs, 66% (two steps); g) *in situ* during reaction or Et_3N, ^{i}PrOH, reflux, 1 hr (preparation of **140**).

Scheme 50. Synthetic route for the formation of **140**, which can also be formed *in situ* using dimer **139** under ATH reaction conditions

The reduction of **49a** was successfully carried out using **140** in formic acid/triethylamine (5:2) azeotrope, giving **49a'** in >99% yield and 96% ee after 18 hrs. The result obtained was comparable to that obtained using the non-tethered analogue, with the same configuration of product formed when the same enantiomer of ligand is used. This shows that the mode of action of the catalyst is unaffected with the presence of the "tether".[25a]

Ruthenium dimer **139** can also be used directly for ATH reductions, as it forms **140** *in situ*. The formation of monomer from dimer involves neutralisation of the salt, splitting of the dimer and wrapping of the ligand around the metal. Reduction of **49a** with dimer

139 in formic acid/triethylamine (5:2) azeotrope, gave **49a'** in >99% yield and 96% ee after 21 hrs (Scheme 51), showing same level of reactivity and enantioselectivity in comparison to **140**, but with a slight increase in reaction time. This induction period is the time required for the conversion of dimer to the monomer. The increased stability given by the "three-point" ligand attachment to the metal was proved by the studies carried out to test the longetivity of **140**. Acetophenone **49a** in addition to formic acid/triethylamine (5:2) azeotrope mixture were added consecutively after completion of each reduction, and after 176 hrs, 3 batches of acetophenone were successfully reduced, without loss of enantioselectivity.[25a]

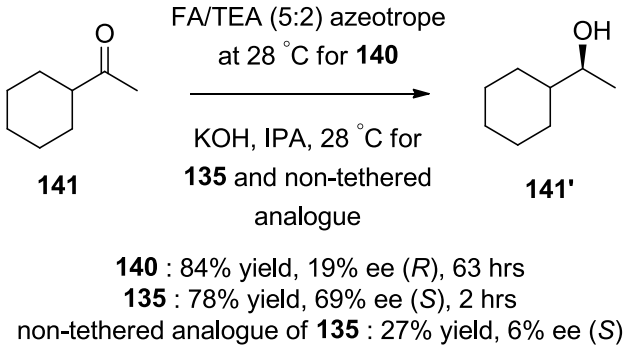


Dimer **139**: >99% yield, 96% ee (*R*), 21 hrs
Monomer **140**: >99% yield, 96% ee (*R*), 18 hrs

Scheme 51. ATH reduction of **49a**, using dimer **139** and monomer **140**.

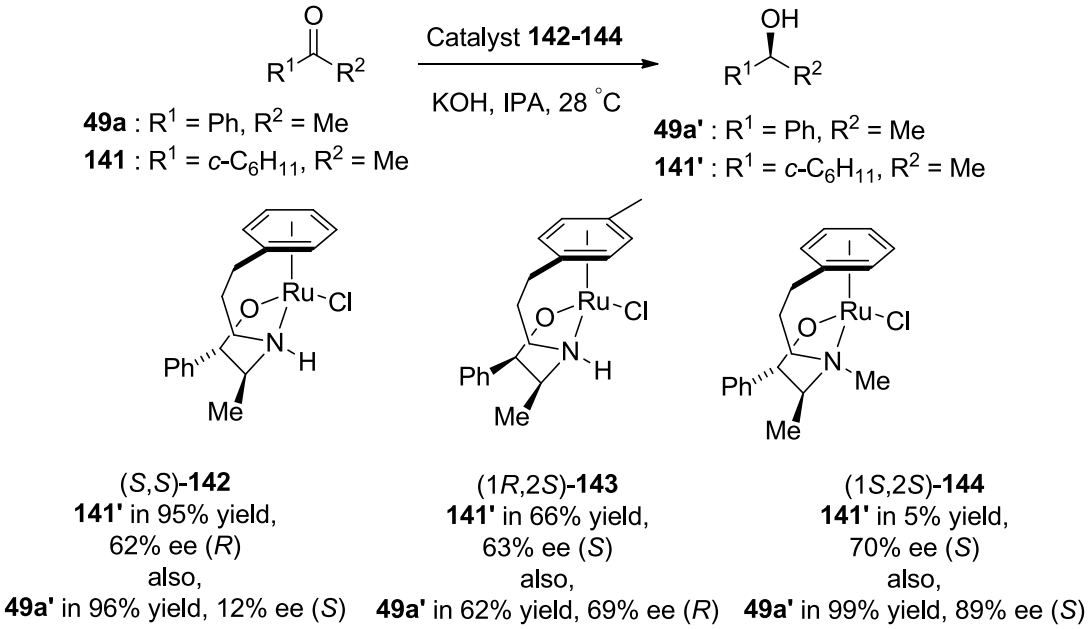
The asymmetric reduction of alkyl/alkyl substituted ketones is known to be a challenging transformation, as the important interaction between the aryl ring of the catalyst and that of the substrate is absent (Section 1.4.5). Reduction of cyclohexylmethyl ketone **141** was carried out to determine whether the "tethering" might have an effect on the enantioselectivity of this process. Using catalyst **140**, the reduction of **141** was successfully achieved in 84% yield after 63 hrs, but the ee obtained was very low (19%). An improved result was obtained using catalyst **135**, giving the reduced product in 78% yield after 2 hrs, but with an improved ee of 69%. The reduction of **141** using the equivalent non-tethered complex [((1*R*,2*S*)-ephedrine)Ru(*p*-cymene)Cl] under the same conditions gave product in 27% yield and 6% ee. The tethering group clearly has a dramatic influence on the selectivity of the

reduction process. To probe this effect catalysts **142-143** were synthesized. The ephedrine unit in **143** was replaced with a pseudoephedrine unit, giving **144**. Catalyst **144** was worthy of investigation as the non-tethered analogue of **144** reported by Noyori ([((1*S*,2*S*)-pseudoephedrine)Ru(C_6Me_6)Cl]), reduced **141**, giving **141'** in 93% yield and 75% ee (*S*) (Scheme 52).[25b]



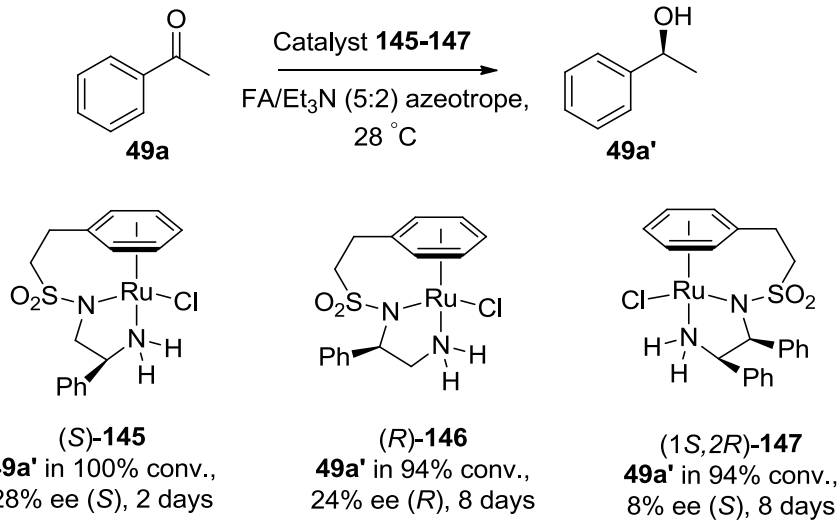
Scheme 52. ATH reduction of **141**, using **140**, **135** and non-tethered analogue of **135**.

The reduction of **141** was effective using catalyst **142** and **143**, but **135** was better overall. Catalyst **144** however did give the highest ee of 70%, but the conversion was poor (5%) (Scheme 53). The reduction of **49a** was also carried out using catalyst **142-144**, with **144** giving the best result (**49a'** in 99% yield and 89% ee).[25b]



Scheme 53. ATH reduction of **49a** and **141**, using catalyst **142-144** (S/C = 200).

The Wills group have previously reported the importance of *trans*-1,2-diphenyl substitution pattern of TsDPEN **81** on the rate and enantioselectivity of the Ru(II) catalysed ATH reactions (Section 1.4.5). Such modifications of complex **140** were examined by synthesizing complex **145-147** (Scheme 54).[25b]



Scheme 54. ATH reduction of **49a**, using complex "tethered" complex **145-147** (S/C = 200).

Complexes **145-147** shown in Scheme 54 were all effective for the reduction of **49a**, giving **49a'** in good conversions, but poor ee's, and long reaction times.[25b]

Restriction of conformations available to the arene ring serves to be one of the major advantages of the "tethering" complex, as this allows selective functionalization to be inserted, with predictable spatial arrangement. Sterically hindered groups can be placed at the *para* position of the metal arene ring (Figure 16), changing the basis of enantiocontrol from electronic to steric in order to target challenging substrates such as **141**. Derivatives of the two "tethering" complex **135** and **140**, containing an aminoalcohol and a sulfonylated diamine respectively were prepared **148-155**. The conventional method approach to synthesize "tethered" catalyst has been to use Birch reduction to prepare the 1,4-cyclohexadiene ring, but for the synthesis of **148-155**, an alternative approach based on [4 + 2] cycloaddition strategy between a diene and a functionalised alkyne was employed. (Scheme 55).[25c]

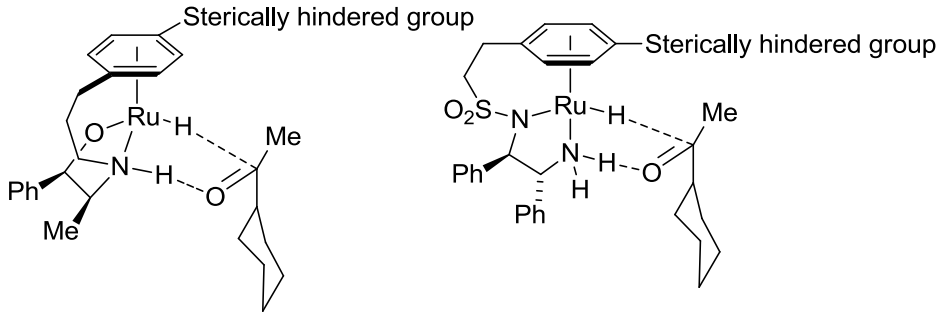
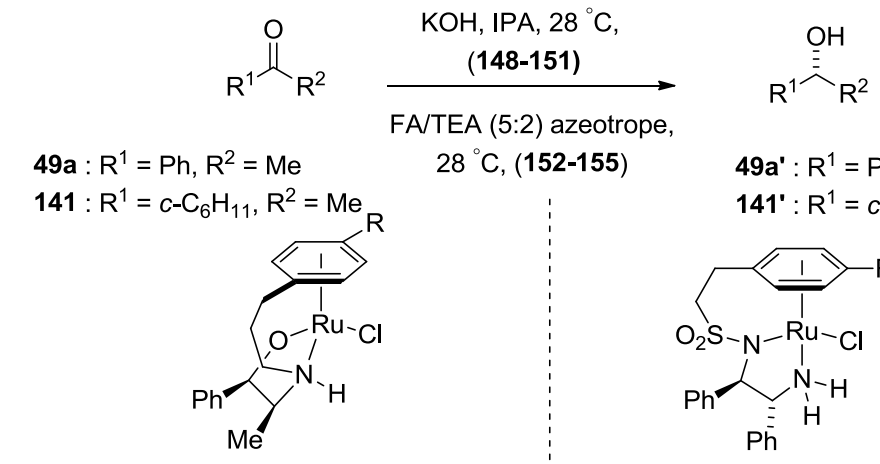


Figure 16. Proposed transition state for the ATH of **141**, using catalyst **148-155**, with a sterically hindered group in the *para* position.

Catalysts **148-151** and **152-155** were tested for the ATH reduction of **49a** and **141**. The reactivity and enantioselectivity obtained for **148-155** were much lower than its parent complexes, possibly due to the increased steric hinderance.[25c]

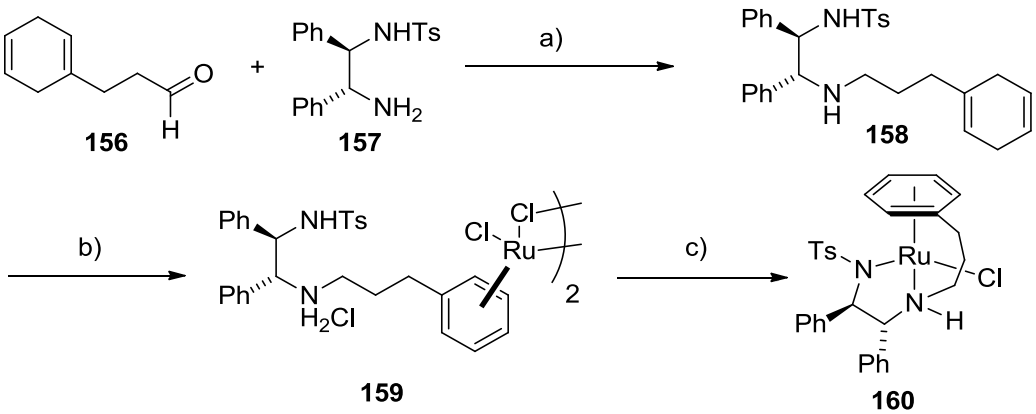


148 : R = Me : **49a'** in 56% conv., 72% ee (*R*)
141' in 22% conv., 62% ee (*S*)
149 : R = ^{t}Bu : **49a'** in 77% conv., 77% ee (*R*)
141' in 15% conv., 45% ee (*S*)
150 : R = Ad : **49a'** in 64% conv., 64% ee (*R*)
141' in 12% conv., 54% ee (*S*)
151 : R = Ph : **49a'** in 37% conv., 37% ee (*R*)
141' in 43% conv., 16% ee (*S*)
Time for **49a'** and **141'** = 2 hrs

152 : R = Me : **49a'** in 88% conv., 63% ee (*R*)
141' in 20% conv., 27% ee (*R*)
153 : R = ^{t}Bu : **49a'** in 35% conv., 35% ee (*R*)
141' in 10% conv., 17% ee (*R*)
154 : R = Ad : **49a'** in 44% conv., 25% ee (*R*)
141' in <10% conv., 18% ee (*R*)
155 : R = Ph : **49a'** in 63% conv., 68% ee (*R*)
141' in 50% conv., 36% ee (*R*)
Time for **49a'** = 96 hrs, and for **141'** = **152** (166 hrs) **153** (72 hrs), **154** (91 hrs) and **155** (72 hrs).

Scheme 55. ATH reduction of **49a** and **141**, using catalyst **148-155** (S/C = 200).

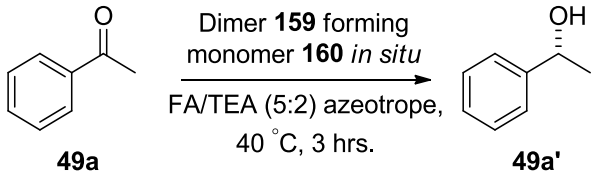
Recently Wills and co-workers had discovered that the "tethered" catalyst based on monosulfonylated diamine, can be significantly improved by attaching the linking group from the "basic" amine rather than the sulfonyl group (as in **140**). The preparation of complex **160**, refered to as "reverse-tethered" has been shown in scheme 56.[25d]



-a) 4 Å mol. sieves, DCM, o/n then $LiAlH_4$, THF, 2 hrs. 47% (over 2 steps); b) HCl, Et_2O then $RuCl_3.H_2O$, EtOH, reflux, o/n, 89% (over 2 steps); c) Et_3N, IPA or formed *in situ* under reduction conditions.

Scheme 56. Synthesis of the "reverse-tethered" catalyst **160**.

Catalyst **160** proved to be highly active as the reduction of acetophenone **49a** was achieved in just 3 hrs, at 40 °C (S/C= 200), giving **49a'** in 96% ee (Scheme 57). The catalyst was also active and equally enantioselective at a loading as low as 0.01 mol%, which is unheard of for this class of ATH catalyst.[25d]

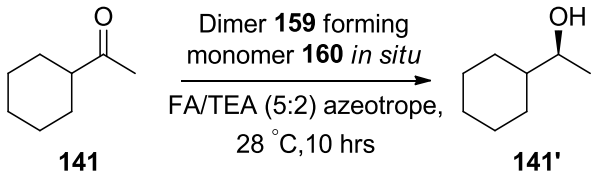


Scheme 57. ATH reduction of **49a**, using dimer **159** forming **160** *in situ* (S/C = 200).

^{1}H NMR studies for the reduction of acetophenone **49a** was carried out at 40 °C using monomer **160**, dimer **159** and untethered catalyst **38** (S/C = 200) in 5:2 formic acid/triethylamine. A mixture of the catalyst in FA/TEA was stirred for 20 mins, followed by the addition of the mixture to an NMR tube along with a small quantity of d_6-benzene and the required quantity acetophenone **49a**. The results showed that the reactivity of **160** and **159** is far greater than untethered catalyst **38**, with the complete reduction of acetophenone **49a** using untethered catalyst **38** being achieved after 18 hrs, **159** after 3 hrs and **160** in 110 minutes. A close examination of the reaction using dimer **159** indicates an initial lag at the start of the reaction, due to the incomplete *in situ* conversion of the dimeric species to the monomer. Repeating the reaction with the dimer **159** being stirred in FA/TEA for 3.5 hrs prior to the addition of ketone, gave complete conversion of acetophenone in 110 minutes, identical to monomer **160**. The

longevity of **160** was also investigated, by consecutive addition of acetophenone **49a** and FA/TEA after completion of each reaction. After seven cycles of acetophenone **49a** addition, the catalyst remained consistently active throughout with no loss of ee.[25e]

Investigation on the reduction of dialkyl ketone was next carried out using catalyst **160**. Cyclohexylmethyl ketone **141** was fully reduced using dimer **159**, giving **141'** in 69% ee at 28 °C (S/C = 200) in 10 hrs (Scheme 58).[25e] In comparison to **140**, which gave **141'** in 84% conversion and 19% ee after 63 hrs at 28 °C.[25b]



Scheme 58. ATH reduction of **141**, using dimer **159** forming **160** *in situ* (S/C = 200).

The "tethering" at the basic amine has tremendously enhanced the enantioselectivity of dialkyl ketones. The configuration obtained for the reduction of cyclohexylmethyl ketone was opposite to that of acetophenone reduction, which indicates that the large cyclohexyl substituent is directed away from the arene ring of the catalyst. It was possible that the "tether" lies in the region occupied by the group on the ketone, repelling the larger alkyl group away from the "tether" (Figure 17, **160**-TS). In order to further investigate this possibility, complex **161** with a dimethyl-substituted "tether" was prepared (Figure 17, **161**), in a similar way to **160**. As the introduction of the dimethyl-substituent would further increase the steric repulsion (Figure 17, **161**-TS), and therefore increase the enantioselectivity.[25e]

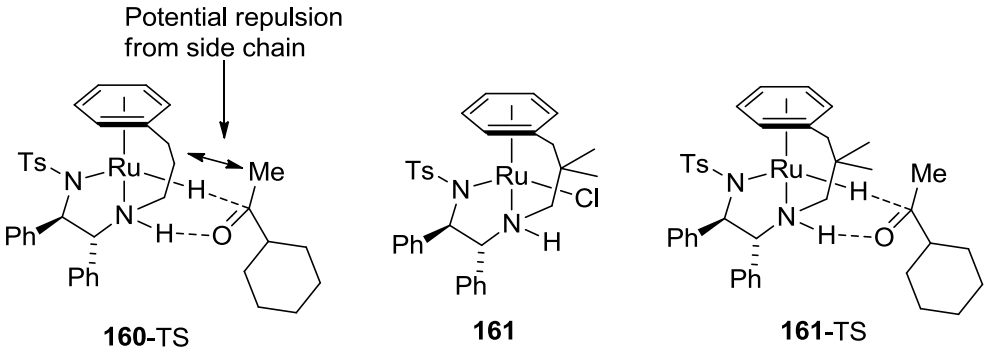
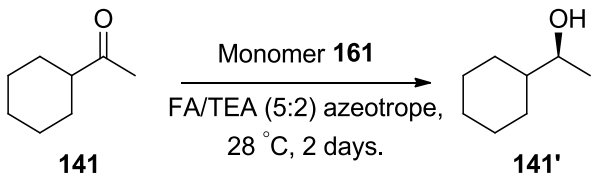


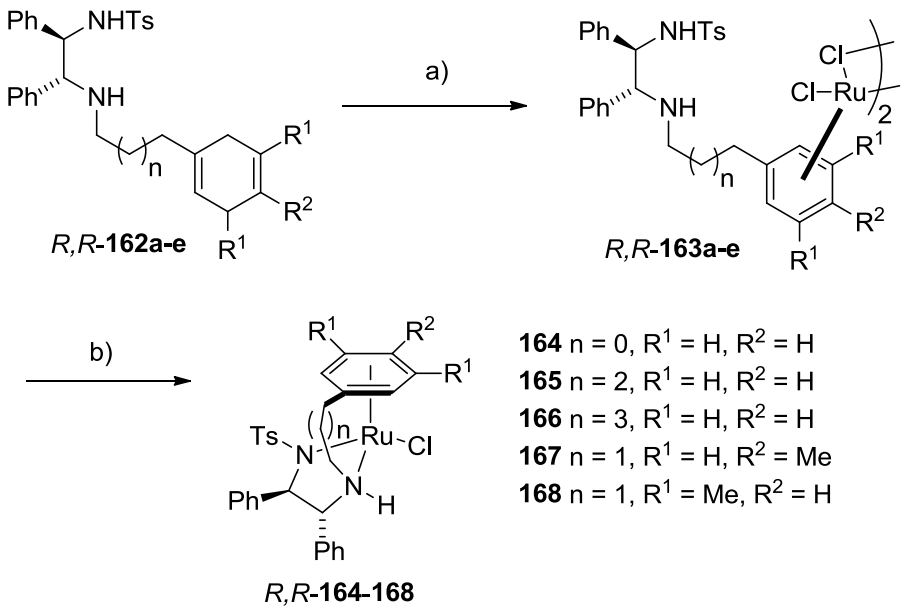
Figure 17. Possible reduction transition state of alkyl/alkyl ketones using **160**, and the predicted transition state of complex **161**.

Introducing dimethyl substitution on the "tethered" monotosylated diamine gave a positive result for the reduction of **141**, as a 5% improvement in ee over **160** to 74% ee was obtained under identical conditions. The rate of reduction was however diminished giving only 48% conversion after 2 days (Scheme 59).[25e]



Scheme 59. ATH reduction of **141**, using monomer **161** (S/C = 200).

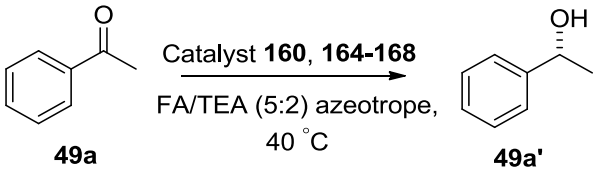
In order to increase the activity and versatility of catalyst **160**, the effects of "tether" length and η^6-arene ring substitution pattern was examined. Complexes **164-168** were identified as a series of systematically modified catalysts worthy of investigation. These complexes were synthesized in good yields via the route shown in Scheme 60.[20a]



a) i) HCl, Et_2O, rt, ii) $RuCl_3$ hydrate, EtOH, reflux, o/n; b) *in situ* during reaction or Et_3N, ^{i}PrOH, reflux, 1-18 hrs.

Scheme 60. Synthesis of "tethered" catalysts **164-168**.

Precursors **162a-e** were obtained after the Birch reduction of its corresponding arenes. The dimers **163a-e** prepared from **162a-e**, can be used directly in ATH reductions, as it forms monomer **164-168** *in situ*, but for accurate comparison and analysis monomer **164-168** were isolated. With the exception of **166**, which has the longest "tether". Monomer formation took place within a few hours from the reaction of dimer with Et_3N in refluxing IPA, but for **163c** only a small quantity of **166** was produced even after extended reaction times. ATH reduction of **49a**, using **160** and **164-168** were carried out at 40 °C (S/C = 200) in FA/TEA (5:2) azeotrope (Scheme 61, Table 18).[20a]



Scheme 61. ATH reduction of **49a**, using catalyst **160**, **164-168** (S/C = 200).

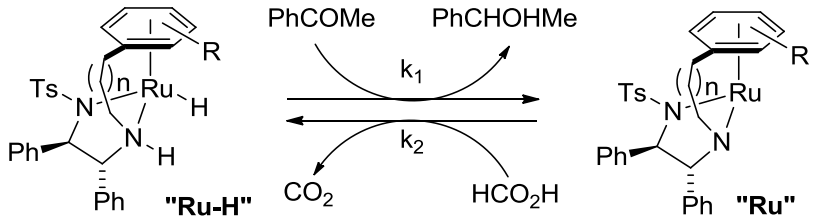
Catalyst	Loading (mol%)	Temp (°C)	Ketone	Time (hrs)	Conv (%)	ee (%) (*R*/*S*)
(*S*,*S*)-160	0.5	40	**49a**	2	100	96 *S*
(*R*,*R*)-164	0.5	40	**49a**	15	19	92 *R*
(*R*,*R*)-165	0.5	40	**49a**	1.25	100	96 *R*
(*R*,*R*)-166	0.5	40	**49a**	6	38	94 *R*
(*R*,*R*)-167	0.5	40	**49a**	4	100	96 *R*
(*R*,*R*)-168	0.5	40	**49a**	5	100	93 *R*

Table 18. ATH reduction of **49a**, using **160** and **164-168** (S/C = 200).

The results obtained from the ATH studies showed that the most active catalyst for the reduction of **49a** was 4C-"tethered" complex **165**, giving full reduction within 75 min with an ee of 96% (*R*). Complex **165** proved to be faster than the previously reported 3C-"tethered" complex **160**, and significantly faster than the 5C **166** and the 2C **164** "tethered" complexes. The ee's obtained using **166** and **164** were high, showing that they are still operating through the transition state expected for these compounds. As a result of this increased activity of **165**, the catalyst loading can be reduced to as low as 0.01 mol%, matching the level at which **160**[25d] has been used.[20a]

Kinetic studies on **160, 83** and **164-168** were carried out at 40 °C using 1.62 M ketone in FA/TEA (S/C = 200), with the conversion being monitored by ^{1}H NMR and chiral GC. The studies showed that catalysts **160**, **164**, **166**, **167** and **168** for majority of the reaction displayed zero-order kinetics, whereas catalyst **165** showed mixed-order kinetics. Analysis of this data was carried out, assuming that ketone reduction by Ru-H species is second-order kinetics and the regeneration of Ru-H by formic acid is first order kinetics. The results revealed that the high rate obtained with catalyst **165** is due to increased rate of hydride regeneration combined with rapid ketone reduction. Noyori's untethered catalyst **83** also showed mixed-order kinetics similar to **165**, but it took 20 hrs to complete the reduction. For other "tethered" catalysts, the overall reduction is

restricted by the rate of hydride regeneration, until the ketone concentration has dropped to low levels. (Scheme 62).[20a]

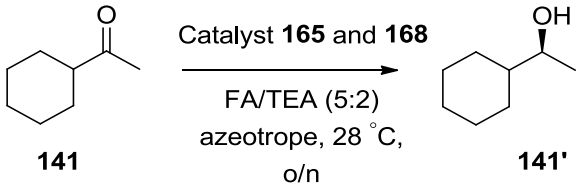


	k_1[a]	k_2[a]
(*S*,*S*)-**160**	10	3.7
(*R*,*R*)-**164**	>0.5	0.034
(*R*,*R*)-**165**	11	9.3
(*R*,*R*)-**166**	>3	0.25
(*R*,*R*)-**167**	11	1.2
(*R*,*R*)-**168**	2.5	1.6
(*R*,*R*)-**83**	0.75	1.0

[a] $M^{-1}min^{-1}$. [b] min^{-1}.

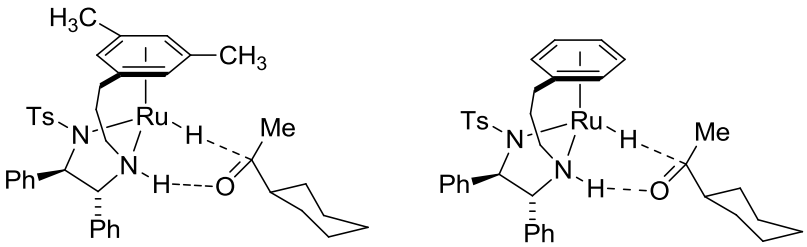
Figure 62. Kinetic data for the reduction of **49a**. Reactions were carried out at 40 °C, [ketone] = 1.62 M, FA/TEA (5:2), S/C = 200.

The reduction of a dialkyl ketone using catalyst **165** and **168** was carried out, with both catalysts fully reducing cyclohexylmethyl ketone **141** overnight. Catalyst **165** gave the product in 66% ee; however catalyst **168** gave a product in 90% ee with the configuration of product obtained in both cases being opposite to that of acetophenone, relative to the diamine configuration (Scheme 63).[20a]



Scheme 63. ATH reduction of **141**, using catalyst **165** and **168** (S/C = 200).

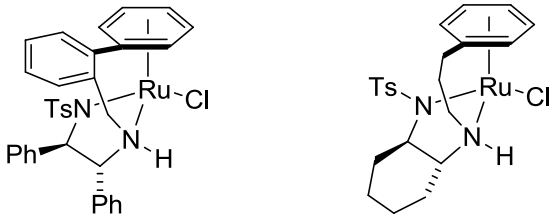
This increased ee using **168** suggests that the extra methyl groups on the η^6-arene ring forces the larger ketone substituent in to the less hindered region (Figure 18). This catalyst was the first example of a Ru/TsDPEN catalyst designed and demonstrated to have useful levels of enantioselectivity for non-aromatic substrates, with the replacement of electronic elements to steric ones.[20a]



(*R*,*R*)-**168** (*R*,*R*)-**160**

Figure 18. Dimethyl substitution on the η^6-arene ring **168** increases steric hinderance, which in effect increases the ee (left; 90% ee) for the reduction of cyclohexylmethyl ketone over **160** (right; 69% ee).

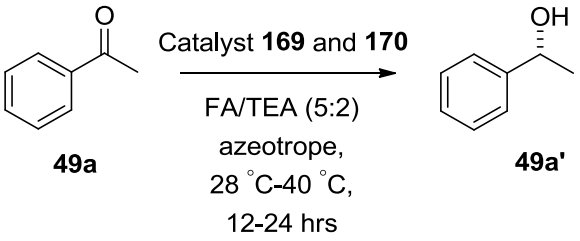
Further investigation on "tethered" catalysts was conducted, where a benzylic "tether" **169**, in place of the aliphatic one was synthesized and tested along with complex **170**, in which the diphenyl substituted diamine ligand **81** is replaced with a homochiral *R*,*R*-1,2-diaminocyclohexane (*R*,*R*-TsCYDN) **91** (Figure 19). Derivatives of 1,2-diaminocyclohexane have been reported to be effective for the reduction of ketones in the untethered form as mentioned earlier in Section 1.4.3.2.[25f]



169 **170**

Figure 19. "Tethered" Ru(II) catalyst **169** and **170**.

Both catalysts demonstrated good activity for the ATH of ketones in FA/TEA, but neither gave an improved performance relative to catalyst **165**. Reduction of **49a** using **169**, gave the alcohol in 100% conv., 95% ee after 24 hrs at 40 °C, and using **170**, in 100% conv., 92% ee after 12 hrs at 28 °C (Scheme 64).[25f]



Scheme 64. ATH reduction of **49a**, using catalyst **169** and **170** (S/C = 200).

The use of ether-linked "tethered" catalysts **171-173** (Figure 20), which have a stereochemically well-defined structure, and in effect controls the configuration at the metal centre were also examined by the Wills group for ATH.[25g]

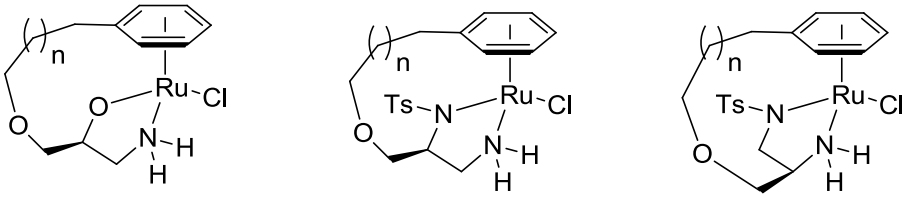
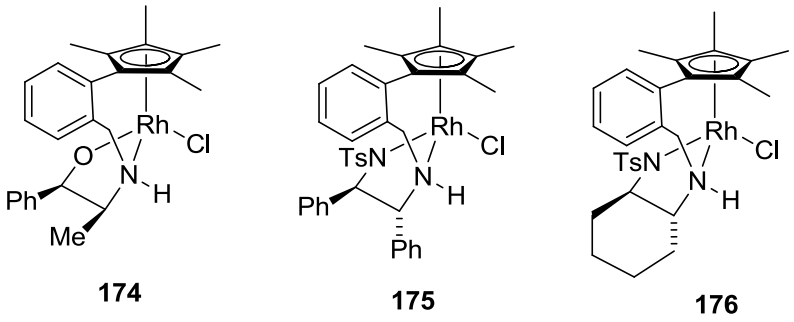


Figure 20. Ether-linked "tethered" catalysts.

The results obtained showed that out of all, **173b** (S/C = 200) proved to be the most active for the ATH reduction of **49a** in FA/TEA (5:2) azeotrope at 40 °C, giving **49a'** in 100% conversion and 29% ee (*R*) after an overnight reaction. This shows that the "tether" length is not interfering with the catalytic mechanism, as the activity of the catalyst is unaffected. The catalyst was however lacking the elements which affect the enantioselectivity of ketone reductions.[25g]

Wills' group have also synthesized "tethered" rhodium catalysts where the *β*-amino alcohol and monotosylated diamine is "tethered" to the cyclopentadienyl group. Although tetramethylcyclopentadienyl group is different in structure to the arene ligand, the same CH/π stabilising effect is known to operate through the methyl groups as shown previously in Section 1.4.5. The first rhodium "tethered" catalyst synthesized

was **174**,[25h] which proved to be a highly active catalyst for ketone reduction, but failed to remain stable under reaction conditions (Figure 21). The reduction of acetophenone **49a** using 1-5 mol% of catalyst **174** and KO*t*-Bu in IPA at rt gave ee of up to 75% and conversion of up to 98% (*R*), but with decreasing ee as the conversion was increasing. Rhodium "tethered" monotosylated diamine catalysts were later prepared **175-176**, which were stable under reactions conditions (using FA/TEA) and showed excellent enantioselectivity and reactivity for a range of ketone reductions. The reduction of **49a** using **175**,[25i] gave the alcohol **49a'** in 100% conv., 98% ee (*R*) within 10 hrs at 25 °C in FA/TEA (S/C = 200), and using **176** in 100% conv., 96% ee (*R*) in just 2 hrs at 28 °C in FA/TEA (S/C = 200).[25j]



174 **175** **176**

Figure 21. Structures of rhodium(III) "tethered" catalysts.

2. Results and Discussion.

2.1 Asymmetric transfer hydrogenation reduction of quinolines using Ru(II) "tethered" catalysts.

Tetrahydroquinoline derivatives have attracted considerable attention owing to their importance as synthetic intermediates for drugs, agrochemicals, and dyes as described earlier in Section 1.3.3.6. Reduction of quinolines to tetrahydroquinolines represents a simple and promising methodology as quinoline derivatives are very easily available. A number of reports on the pressure hydrogenation of quinolines have been published, but very little research has been carried out on the transfer hydrogenation of quinolines (Section 1.4.6.5). It would be of great interest to know whether asymmetric transfer hydrogenation of quinolines can be successfully carried out using "tethered" and untethered Ru(II) catalysts in FA/TEA, as this method if successful, would ensure formation of the desired product under mild conditions.

In the preliminary studies carried out for the ATH reduction of quinolines, Blackmond's reported method was used,[23j] whereby formic acid was added in dropwise by syringe over a duration of 30 mins to a mixture of 4C 'tethered' dimer **163b**, triethylamine and the substrate **120a, 115a, 177-181** (Figure 22) dissolved in methanol.

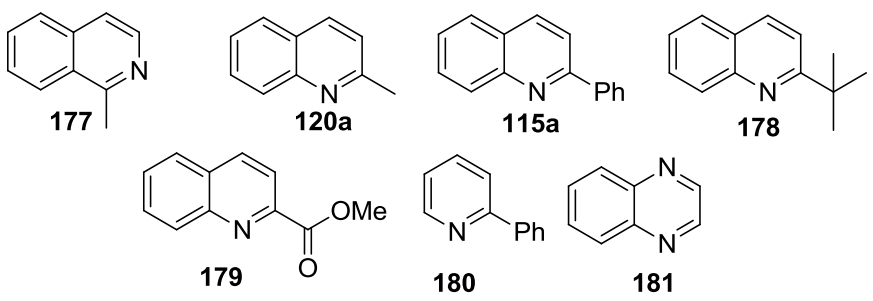


Figure 22. Substrates that were used for preliminary studies.

In the previous studies, Wills group had demonstrated that monomer catalysts are formed *in situ* from their dimer precursors (Section 1.4.7). For this reason, a mixture of monomer and dimer catalysts was used (Figure 23), the selection of which depended on their availability and diversity of structure. However, most of the reductions that were conducted on quinolines employed the 4C 'tethered' dimer **163b**, which is converted *in situ* into the monomer **165**.

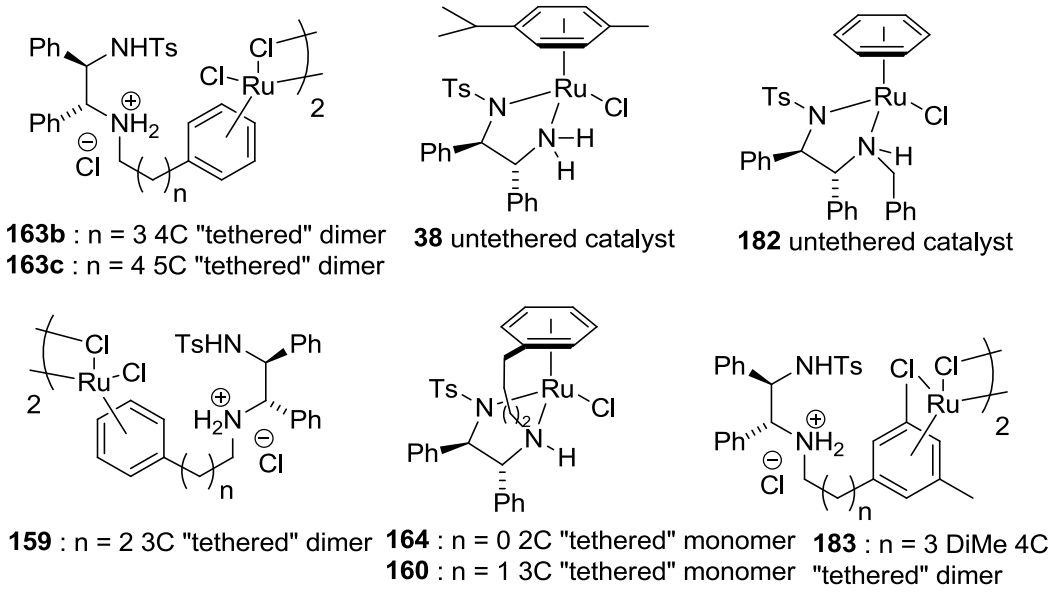


Figure 23. Ru(II) catalysts that were used for the ATH of quinolines.

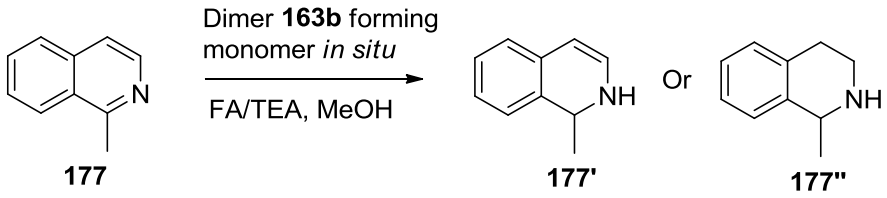
The first step in this project was to investigate the ATH reduction of isoquinoline, quinoline and quinoxaline rings using the 4C 'tethered' dimer **163b**.

2.1.1 Preliminary studies.

ATH reduction of isoquinolines.

ATH reduction was carried out on 1-methylisoquinoline **177** using catalyst **163b**, giving <5% conversion of a non-identified product after 24 hrs (Table 19, Scheme 65). This

result shows that the current method used is not suitable for the reduction of isoquinoline substrates.



Scheme 65. ATH of 1-methylisoquinoline **177** using dimer **163b**.

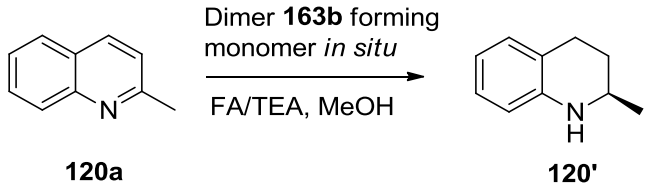
Imine	Catalyst	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
177	**(*R*,*R*)-163b**	rt	24	-	- -

Table 19. ATH reduction of 1-methylisoquinoline **177** to give **177'** or **177''**

(Concentration of 0.22 M with respect to imine, dropwise-method of FA employed, FA/TEA (5:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

ATH reduction of quinolines.

The next step was to carry out the ATH reduction on 2-methylquinoline **120a**, which gave a positive result as **120a** was reduced to give 2-methyl-1,2,3,4-tetrahydroquinoline **120a'** in 47% conversion and 50% ee after 96 hrs (Scheme 66, Table 20).

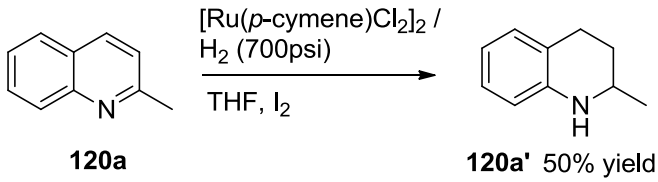


Scheme 66. ATH reduction of 2-methylquinoline **120a** using dimer **163b**.

Imine	Catalyst	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
120a	**(*R*,*R*)-163b**	rt	96	47	50 *R*

Table 20. ATH reduction of 2-methylquinoline **120a** to tetrahydroquinoline **120a'** (Concentration of 0.22 M with respect to imine, dropwise-method of FA employed, FA/TEA (5:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

The result obtained was quite encouraging and represented a good starting point in this project. The racemic standard was obtained by injecting **120a** in THF to a solution of $[Ru(p\text{-cymene})Cl_2]_2$ and I_2 dissolved in THF, after which pressure hydrogenation on the mixture was carried out at 700 psi for 24 hrs giving the racemic 2-methyl-1,2,3,4-tetrahydroquinoline **120a'** in 50% yield (Scheme 67). The ee of the ATH product was obtained by GC, comparing the starting material **120a**/racemic standard[10b] with the asymmetric product **120a'**.



Scheme 67. Pressure hydrogenation of **120a** giving a racemic product **120a'**, using $[Ru(p\text{-cymene})Cl_2]_2$.

ATH reduction of 2-methylquinoline; increasing the quantity of formic acid.

The next objective was to start optimizing the conditions using 2-methylquinoline as a model substrate to achieve a conversion that is acceptable before focusing on increasing the enantioselectivity.

The first optimization was carried out by increasing the quantity of formic acid injected into the solution, as FA decomposes over time and may also act as a protonating source for the C=C bond, more acid may be required for the reaction to go to completion.

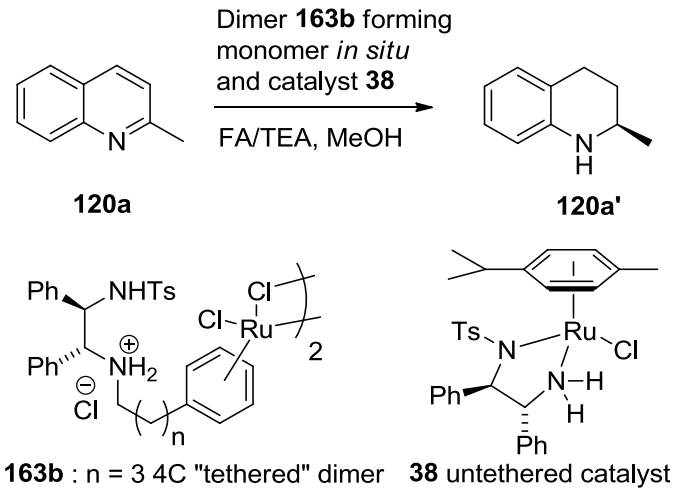
Imine	Catalyst	FA/TEA ratio	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
120a	**(*R*,*R*)-163b**	5:2	rt	72	36	48 *R*
120a	**(*R*,*R*)-163b**	10:2	rt	72	>99	50 *R*
120a	**(*R*,*R*)-163b**	15:2	rt	66.5	94	48 *R*

Table 21. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.22 M and 0.22 M with respect to imine, dropwise-method of FA employed, FA/TEA (5:2, 10:2 and 15:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

The results (Table 21) clearly show that changing the formic acid: triethylamine ratio from 5:2 to 10:2 leads to the complete conversion of **120a** to give (*R*)-2-methyl-1,2,3,4-tetrahydroquinoline **120a'** (Scheme 66) with 50% ee. Changing the ratio further to 15:2 gives a respectable conversion of 94% and 48% ee after 67 hrs which would possibly reach >99% conversion by 72 hrs.

ATH reduction of 2-methylquinoline; comparison of the 4C "tethered" catalyst 163b with the untethered catalyst 38.

The next task was to see how active the 4C "tethered" catalyst **163b** is in comparison to the untethered catalyst **38**, and whether or not the ee obtained using catalyst **38** is any different to that obtained using catalyst **163b** (Scheme 68).



Scheme 68. ATH reduction of 2-methylquinoline **120a** using catalyst **163b** and **38**.

Imine	Catalyst	FA/TEA ratio	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
120a	**(*R*,*R*)-163b**	15:2	rt	186	>99	50 *R*
120a	**(*R*,*R*)-38**	15:2	rt	186	20	77 *R*

Table 22. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.21M with respect to imine, dropwise-method of FA employed, FA/TEA (15:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400) and catalyst **38** (S/C = 200).

The two reactions (Scheme 68, Table 22) were carried out parallel to each other, and the result of the reduction of **120a** with catalyst **163b** using 15:2 FA:TEA shown previously (Table 21) is from this experiment (Table 22).

The results (Table 23, Figure 24) show that catalyst **163b** is much more active than catalyst **38** when it comes to conversion as >99% conversion was obtained after 186 hours with catalyst **163b**, and only 20% conversion was obtained after 186 hours with catalyst **38**, but the ee obtained with catalyst **38** was much higher than that obtained with catalyst **163b**, as 50% ee was obtained with catalyst **163b**, but in a high 77% ee, was obtained with catalyst **38** (Table 22), meaning the 4C link is vital for rapid conversion but having a *p*-cymene arene group on the Ru is essential for achieving high enantioselectivity (Scheme 68).

Time (hrs)	Conversion (%)	
	4C "tethered" catalyst **163b**	Untethered catalyst **38**
0.5	6	1
17	33	2
20	40	2
23.25	45	2
41	71	3
46.5	79	4
66.5	94	6
186	>99	20

Table 23. Conversion of catalyst **163b** vs. **38** over time.

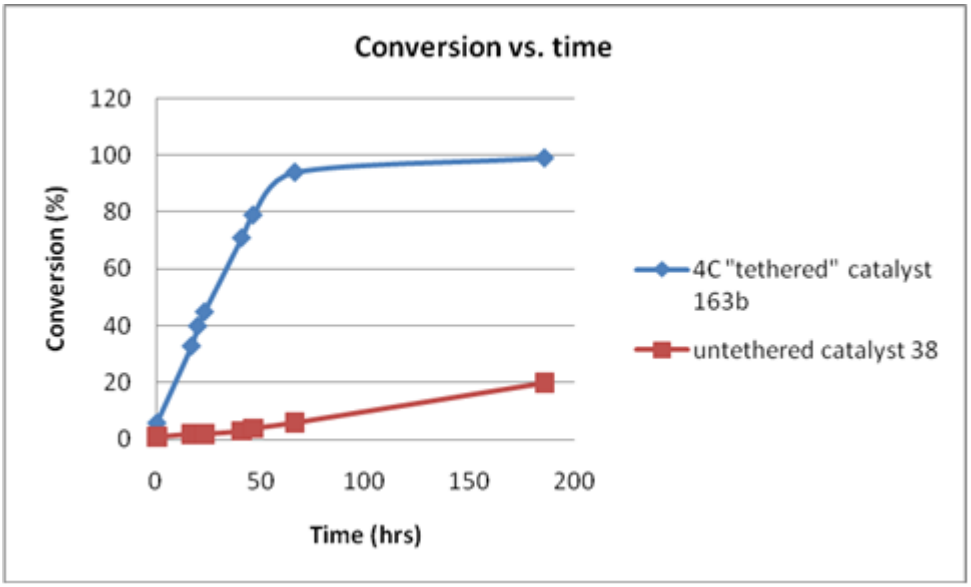
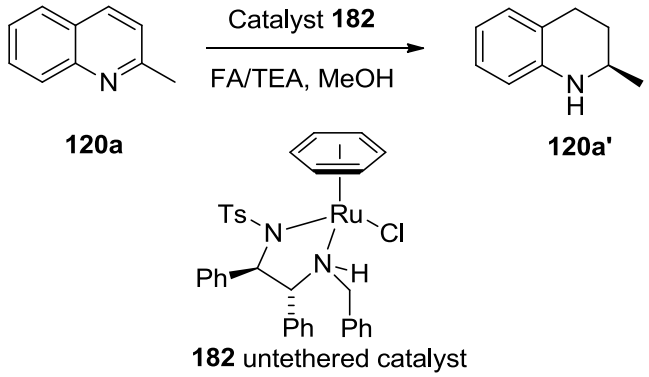


Figure 24. Comparing the conversion of 4C "tethered" catalyst **163b** vs. untethered catalyst **38** over time.

ATH reduction of 2-methylquinoline; 4C "tethered" catalyst 163b vs untethered catalyst 38 vs untethered catalyst 182.

In the previous comparison it was obvious how active catalyst **163b** was when compared to catalyst **38**, so at this point it was decided to see whether or not the untethered catalyst **182**,[17j, 26a] which is known for reducing cyclic imines with great conversion and enantioselectivity and with a higher enantioselectivtiy than **38**, shows any form of increased activity and enantioselectivity for quinoline reduction (Scheme 69, Table 24).



Scheme 69. ATH reduction of 2-methylquinoline **120a** using catalyst **182**.

Imine	Catalyst	FA/TEA ratio	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
120a	**(*R*,*R*)-163b**	15:2	rt	23.25	45	50 *R*
120a	**(*R*,*R*)-38**	15:2	rt	23.25	2	- -
120a	**(*R*,*R*)-182**	10:2	rt	22.25	4	- -

Table 24. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (15:2 and 10:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400) or catalyst **38**/**182** (S/C = 200).

The results showed that catalyst **182,** with a conversion of 4% after 22 hrs, is more active than catalyst **38** with a conversion of 2% after 23 hrs, but clearly catalyst **163b** is even more active, giving a conversion of 45% after 23 hrs and 50% ee (Table 24, Scheme 69).

ATH reduction of 2-methylquinoline; increasing the overall volume of formic acid:triethylamine.

Since the formic acid: triethylamine ratio had been studied, seeing whether increasing the overall volume of triethylamine has any effect on the ATH reduction was examined (Scheme 66, Table 25).

Imine	Catalyst	FA/TEA ratio	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
120a	**(*R*,*R*)-163b**	15:6	rt	176.5	96	42 *R*

Table 25. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.19 M with respect to imine, dropwise-method of FA employed, FA/TEA (15:6)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

The results (Table 25) show that increasing the amount of triethylamine gives a good conversion of 96% after 177 hrs, but an ee of 42% (drop of 8%) was obtained in comparison to the previously obtained ee of 50% (Table 21, 22).

ATH reduction of 2-methylquinoline; using a different solvent.

The final optimization involved the ATH reduction of 2-methylquinoline **120a** using toluene instead of methanol and to use no solvent (Scheme 66, Table 26).

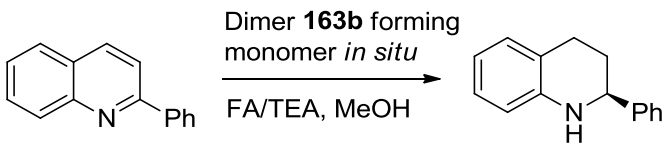
Imine	Catalyst	Solvent	FA/TEA ratio	Temp (°C)	Time (hrs)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
120a	**(*R*,*R*)-163b**	Toluene	10:2	rt	103.5	68	51 *R*
120a	**(*R*,*R*)-163b**	-	10:2	rt	103.5	61	46 *R*

Table 26. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.21M and 1.48 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

In this final optimization it was quite clear that methanol is a better solvent for ATH reduction of quinolines, as the ee obtained with toluene (51%) and no solvent (46%) is comparable with methanol (50%), the conversion using methanol however is much faster (>99% conversion, 72 hrs, Table 21) than using toluene (68% conversion, 104 hrs, Table 26) or no solvent (61% conversion, 104 hrs, Table 26).

ATH reduction of 2-phenylquinoline.

ATH reduction was next carried out on a bulkier substituted quinoline **115a**, as some work has now been carried out on optimizing the reactions (Scheme 70, Table 27).



115a **115a'**

Scheme 70. ATH reduction of 2-phenylquinoline **115a** using dimer **163b**.

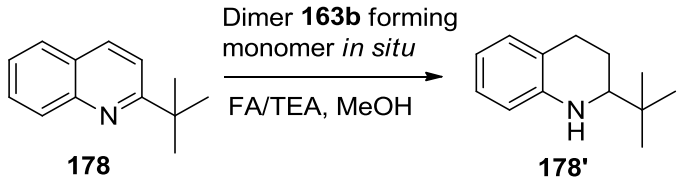
Imine	Catalyst	FA/TEA ratio	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
115a	**(*R*,*R*)-163b**	10:2	rt	107.3	84	64 *S*

Table 27. ATH reduction of **115a** to tetrahydroquinoline **115a'** (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

Reduction of 2-phenylquinoline **115a** was carried out successfully to give (*S*)-2-phenyl-1,2,3,4-tetrahydroquinoline **115a'** with 84% conversion and 64% ee after 107 hrs (Table 27). This is a positive result in addition to what has been obtained with the ATH reduction of 2-methylquinoline **120a**. The configuration was determined by HPLC data comparison with literature.[10d]

ATH reduction of 2-*tert*-butylquinoline.

ATH was carried out on 2-*tert*-butylquinoline **178**, synthesized successfully by cleanly converting *o*-nitrobenzaldehyde to *o*-aminobenzaldehyde using iron metal (10 eq.) in the presence of aq. HCl (20 mol%) in refluxing EtOH for 30 mins. The solids were removed by filtration and the filtrate was treated with 3,3-dimethylbutan-2-one and powdered KOH (3 eq.). After stirring at reflux for 40 mins, 2-*tert*-butylquinoline was obtained with >99% yield.[26b] As **178** is another bulky substrate like **115a**, it was considered interesting to establish whether ATH gives a similar result to what was obtained for the reduction of **115a** (Scheme 71, Table 28).



178 **178'**

Scheme 71. ATH reduction of 2-*tert*-butylquinoline **178** using dimer **163b**.

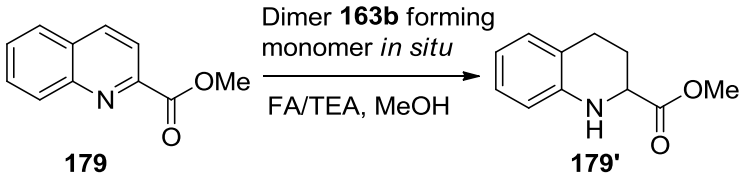
Imine	Catalyst	FA/TEA ratio	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
178	**(*R*,*R*)-163b**	10:2	rt	120.75	77	0 -

Table 28. ATH reduction of **178** to tetrahydroquinoline **178'** (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

2-*tert*-Butylquinoline **178** was successfully reduced to give 2-*tert*-butyl-1,2,3,4-tetrahydroquinoline **178'** with 77% conversion after 121 hrs, but unfortunately a racemic product was obtained (Table 28).

ATH reduction of methylquinoline-2-carboxylate.

The next task was to examine methylquinoline-2-carboxylate **179** reduction by ATH (Scheme 72, Table 29).



179 **179'**

Scheme 72. ATH reduction of methylquinoline-2-carboxylate **179** using dimer **163b**.

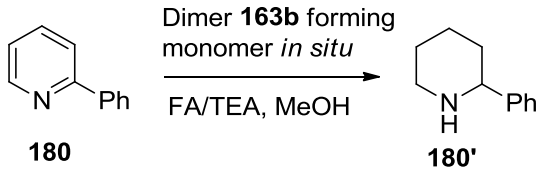
Imine	Catalyst	FA/TEA ratio	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
179	**(*R*,*R*)-163b**	10:2	rt	96	0	- -

Table 29. ATH reduction of **179** to tetrahydroquinoline **179'** (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

Reduction of **179** was unsuccessful (Table 29), possibly due to the interaction of the carboxylate group with the catalyst **163b**, preventing the catalyst **163b** from carrying out the reduction.

ATH reduction of 2-phenylpyridine.

As it was established that quinoline type substrates can be reduced via ATH, attention turned to a test of ATH on the pyridine substrate 2-phenylpyridine **180** (Scheme 73, Table 30).



Scheme 73. ATH reduction of 2-phenylpyridine **180** using dimer **163b**.

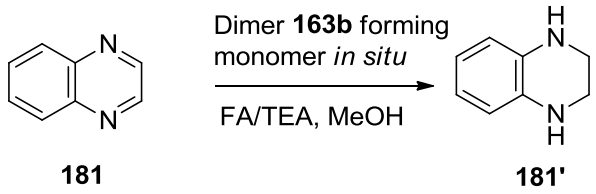
Imine	Catalyst	FA/TEA ratio	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
180	**(*R*,*R*)-163b**	10:2	rt	96	0	- -

Table 30. ATH reduction of **180** to piperidine **180'** (Concentration of 0.21 M with respect to imine, dropwise method of FA employed, FA/TEA (10:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

The reduction on **180** was unsuccessful (Table 30), possibly due to the substrate being far too stable and is able to restore its aromaticity.

ATH reduction of quinoxaline.

Another substrate on which ATH was evaluated was quinoxaline **181**. Although the reaction does not give an asymmetric product, a successful application could be extended to a prochiral substrate. (Scheme 74, Table 31).



Scheme 74. ATH reduction of quinoxaline **181** using dimer **163b**.

Imine	Catalyst	FA/TEA ratio	Temp (°C)	Time (hrs)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
181	**(*R*,*R*)-163b**	10:2	rt	96	17	- -

Table 31. ATH reduction of **181** to tetrahydroquinoxaline **181'** (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

Reduction on **181** was partially successful giving 1,2,3,4-tetrahydroquinoxaline **181'** in 17% conversion (Table 31).

The preliminary studies carried out above was using the dropwise addition of formic acid, and as complete conversion was taking up to 72 hrs, the Noyori method was tested for comparison (Scheme 66, Table 32). In this method, the azeotrope is used from the outset of the reaction.[22]

Imine	Catalyst	Solvent	FA/TEA ratio	Temp (°C)	Time (hrs)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
120a	**(*R*,*R*)-163b**	MeOH	5:2	28	24	96	46 *R*

Table 32. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **163b** forming monomer *in situ* (S/C = 400).

Imine	Catalyst	Solvent	FA/TEA ratio	Temp (°C)	Time (hrs)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
120a	**(*R*,*R*)-163b**	MeOH	10:2	rt	72	>99	50 *R*

Table 33. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer **163b** forming monomer *in situ* (S/C = 400).

The results show (Table 32, 33) that changing the concentration of solution from 0.21 M to 0.45 M with respect to the imine speeds up the reaction rate and the tetrahydroquinoline is formed with complete conversion within 24 hrs.

It is after this point where all the ATH reductions that were carried out were using the non-dropwise method, since it is practically easier and more efficient.

2.1.2 ATH reduction of 2-methylquinoline; optimization of solvent.

In order to optimize the outcome of the reaction, systematic variation of the conditions was carried out using **120a** as a model substrate and **163b** as catalyst (Scheme 66). The results of solvent variation are shown (Table 34).

Imines	Solvent	Temp (°C)	Catalyst	FA/TEA ratio	Time (hrs)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
120a	MeOH	28	**(*R*,*R*)-163b**	5:2	24	96	46 *R*
120a	ACN	28	**(*R*,*R*)- 163b**	5:2	24	79	36 *R*
120a	Water	28	**(*R*,*R*)- 163b**	5:2	24	23	32 *R*
120a	EtOH	28	**(*R*,*R*)- 163b**	5:2	24	96	37 *R*
120a	DCM	28	**(*R*,*R*)- 163b**	5:2	24	92	25 *R*
120a	Et_2O	28	**(*R*,*R*)- 163b**	5:2	24	98	17 *R*
120a	Acetone	28	**(*R*,*R*)- 163b**	5:2	24	8	8 *R*
120a	Toluene	28	**(*R*,*R*)- 163b**	5:2	24	73	22 *R*
120a	IPA	28	**(*R*,*R*)- 163b**	5:2	24	98	31 *R*
120a	EtOAc	28	**(*R*,*R*)- 163b**	5:2	24	74	18 *R*

Table 34. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **163b** forming monomer *in situ* (S/C = 400).

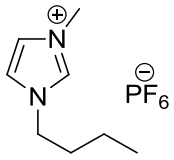
The results clearly show that methanol overall proved to be the best solvent giving a respectable conversion of 96% and 46% ee after 24 hrs (Table 34). The reaction conversions were monitored after 2,4,6 and 24 hrs (Table 36, Figure 25).

ATH of quinolines was also carried out using ionic liquid as solvent instead of methanol to see if that has any effect on the conversion or enantioselectivity (Scheme 66, Table 35). Chan in 2008 reported the reduction of quinolines using Ru(II) catalysts where ionic liquid (Section 1.3.3.6) was used as solvent and up to 99%> conversion and ee was obtained with pressure hydrogenation.

Imines	Solvent	Temp (°C)	Catalyst	FA/TEA ratio	Time (days)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
120a	[BMIM]PF_6	28	**(*R*,*R*)-163b**	5:2	3	88	41 *R*
120a	MeOH/[BMIM]PF_6	28	**(*R*,*R*)-163b**	5:2	5	91	52 *R*

Table 35. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **163b** forming monomer *in situ* (S/C = 400).

[BMIM]PF_6:



Ionic liquid as solvent and using a 50:50 mixture of ionic liquid and methanol gave good results, but methanol alone proved to be the better solvent (Table 35).

Time	Conversion (%)									
(hrs)	MeOH	ACN	H_2O	EtOH	DCM	Et_2O	Acetone	Toluene	IPA	EtOAc
0	0	0	0	0	0	0	0	0	0	0
2	27	47	16	30	51	68	6	34	25	38
4	52	58	23	59	70	73	6	47	52	51
6	76	66	23	79	78	82	6	55	74	58
24	96	79	23	96	92	98	8	73	98	74
	46% ee	36% ee	32% ee	37% ee	25% ee	17% ee	8% ee	22% ee	31% ee	18% ee

Table 36. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **163b** forming monomer *in situ* (S/C = 400). Conversion monitored after 2,4,6 and 24 hrs.

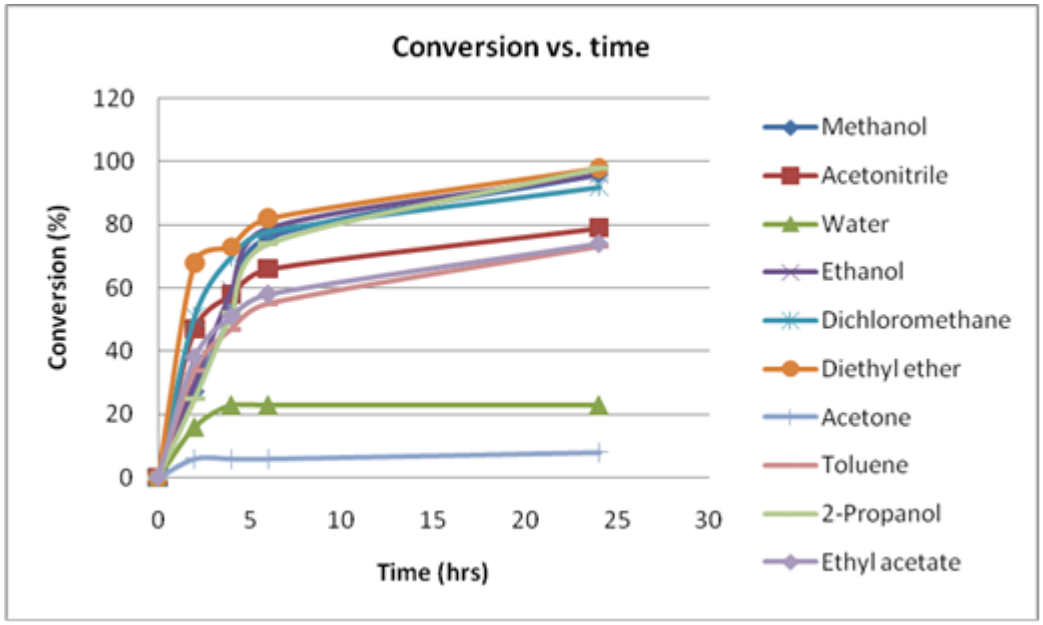


Figure 25. A graph to show conversion vs. time when using different solvents for the ATH reduction of 2-methylquinonline **120a** to tetrahydroquinoline **120a'**.

2.1.3 ATH reduction of 2-methylquinoline; optimization of temperature.

Since methanol was confirmed to be the best solvent, the reactions were next carried out at different temperatures (Scheme 66, Table 37).

Imines	Solvent	Temp (°C)	Catalyst	FA/TEA ratio	Time (hrs)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
120a	MeOH	28	**(*R*,*R*)-163b**	5:2	24	96	46 *R*
120a	MeOH	40	**(*R*,*R*)-163b**	5:2	24	94	44 *R*
120a	MeOH	50	**(*R*,*R*)-163b**	5:2	24	94	43 *R*
120a	MeOH	60	**(*R*,*R*)-163b**	5:2	24	96	43 *R*

Table 37. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **163b** forming monomer *in situ* (S/C = 400).

The results show that the reduction of **120a** to the tetrahydroquinoline **120a'** is most rapid when the reaction is carried out at 60 °C with a drop of 3% ee (Table 37). The reaction conversions were monitored after 2,4,6 and 24 hrs (Table 38, Figure 26).

Time (hrs)	Conversion (%)			
	28 °C	40 °C	50 °C	60 °C
0	0	0	0	0
2	27	74	87	88
4	52	89	89	90
6	76	91	90	91
24	96	94	94	96
	46% ee	44% ee	43% ee	43% ee

Table 38. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **163b** forming monomer *in situ* (S/C = 400). Conversion monitored after 2,4,6 and 24 hrs.

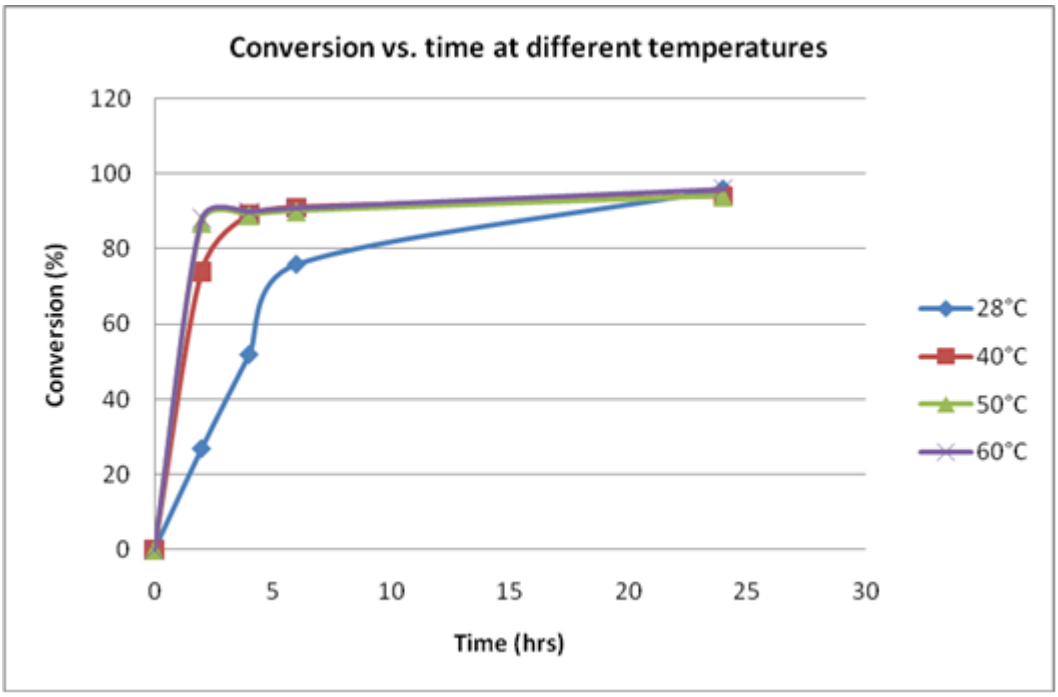
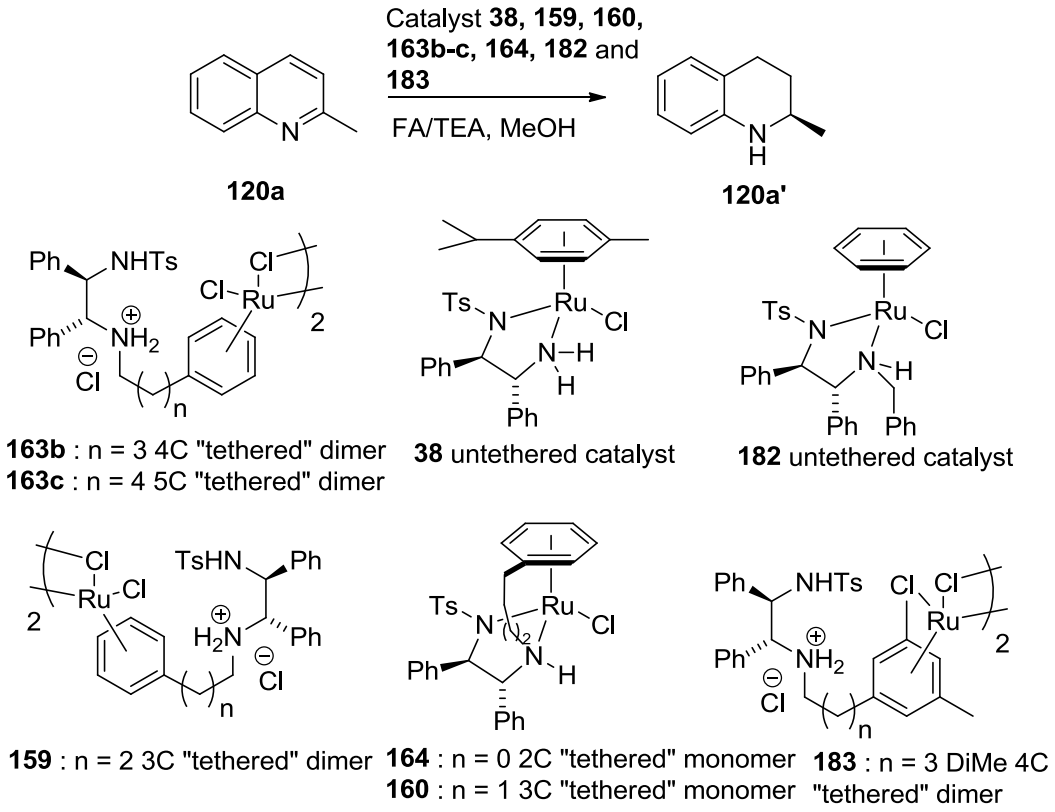


Figure 26. A graph to show conversion vs. time when carrying out ATH reduction of 2-methylquinoline **120a** to tetrahydroquinoline **120a'** at different temperatures.

2.1.4 ATH reduction of 2-methylquinoline; using different catalysts.

As now the optimization with temperature was carried out, it was worth testing out ATH using various catalysts (Scheme 75, Table 39) at 60 °C, as this will increase the rate of conversion even for the less active catalysts quite rapidly with only a loss of 3% ee. This would give a good picture for the final conversion/ee that could be obtained with the catalysts **38, 159, 160, 163b-c, 164, 182** and **183.**



Scheme 75. ATH reduction of 2-methylquinoline **120a**, using catalysts **38, 159, 160, 163b-c, 164, 182** and **183.**

Imines	Solvent	Temp (°C)	Catalyst	FA/TEA ratio	Time (hrs)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
120a	MeOH	60	**(*R*,*R*)-163b**	5:2	24	96	43 *R*
120a	MeOH	60	**(*R*,*R*)-38**	5:2	24	17	80 *R*
120a	MeOH	60	**(*R*,*R*)-182**	5:2	24	66	29 *R*
120a	MeOH	60	**(*R*,*R*)-163c**	5:2	24	87	44 *R*
120a	MeOH	60	**(*S*,*S*)-159**	5:2	24	62	43 *S*
120a	MeOH	60	**(*R*,*R*)-164**	5:2	24	27	68 *R*
120a	MeOH	60	**(*R*,*R*)-160**	5:2	24	59	43 *R*
120a	MeOH	60	**(*R*,*R*)-183**	5:2	24	30	46 *R*

Table 39. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **159**, **163b-c** and **183** forming monomer *in situ* (S/C = 400) and catalyst **38**, **160**, **164** and **182** (S/C = 200).

The results obtained are very encouraging and similar to what was observed in the preliminary studies. Catalyst **163b** is the most active catalyst when compared to the other catalysts used, giving the fastest and the most conversion. The reaction conversions were monitored after 2, 4, 6 and 24 hrs (Table 40, Figure 27). Catalyst **38** however gave the best ee of 80% (Table 39), and yet again it is worth pointing out the fact that it is the only catalyst in the list to have a functionalized aromatic ring on the Ru. In view of the high conversion in the reduction of **120a** achieved using the 4C 'tethered' complex **163b**, but the high ee of 80% achieved using the *p*-cymene containing untethered complex **38**, catalyst **183** was synthesized, which contains elements of each in order to achieve both high activity and enantioselectivity. This catalyst contains a methyl group in the arene ring, intended to mimic the *p*-cymene ring in **38**, which was considered to be important for high enantioselectivity. Catalyst **183** however proved to be unsuccessful as it did not prove to be as active as catalyst **163b**

and it was not able to achieve enantioselectivity near enough catalyst **38** as a conversion of 30% and an ee of 46% was obtained after 24 hrs at 60 °C (Table 39).

Time (hrs)	Conversion (%)							
	4C dimer **163b**	Unteth. catalyst **38**	Unteth. catalyst **182**	5C dimer **163c**	3C dimer **159**	2C monomer **164**	3C monomer **160**	4C DiMe dimer **183**
0	0	0	0	0	0	0	0	0
2	88	13	46	45	47	3	50	18
4	90	15	58	77	51	5	53	21
6	91	16	61	83	53	8	54	24
24	96	17	66	87	62	27	59	29
	43% ee	**80% ee**	**29% ee**	**44% ee**	**43% ee**	**68% ee**	**43% ee**	**42% ee**

Table 40. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **159**, **163b-c** and **183** forming monomer *in situ* (S/C = 400) and catalyst **38**, **160**, **164** and **182** (S/C = 200). Conversion monitored after 2,4,6 and 24 hrs.

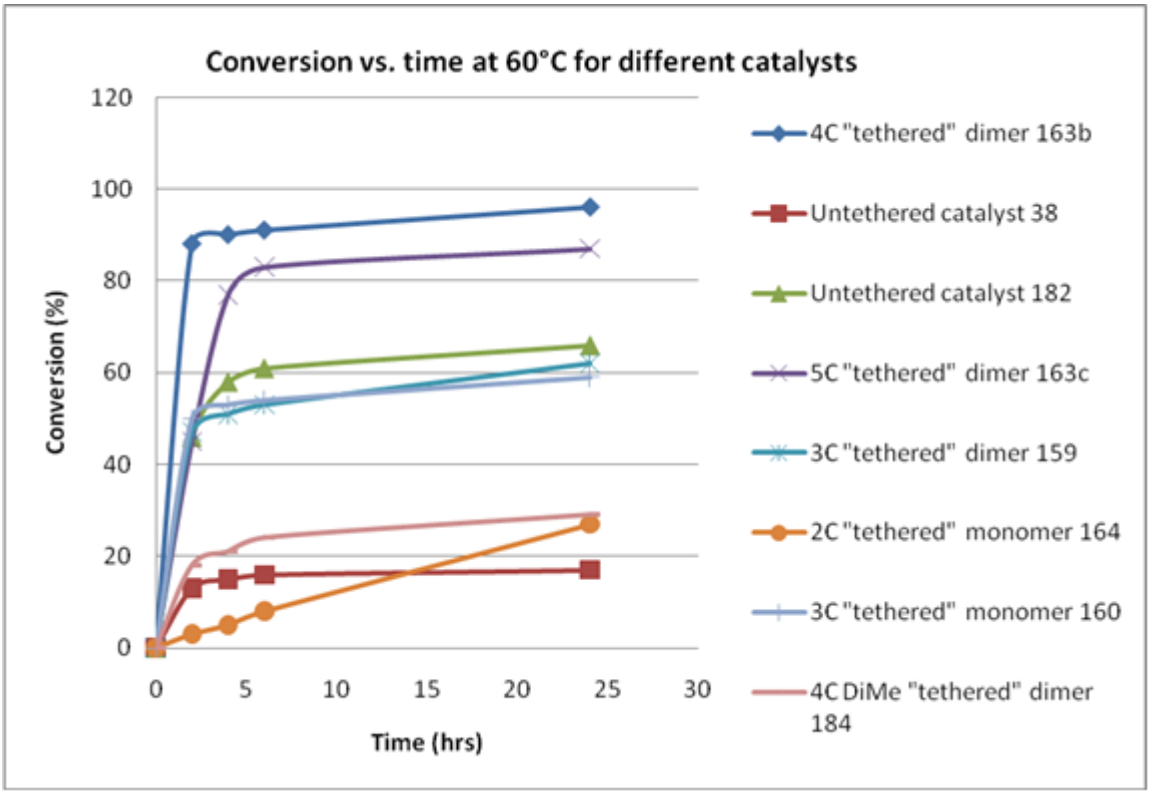
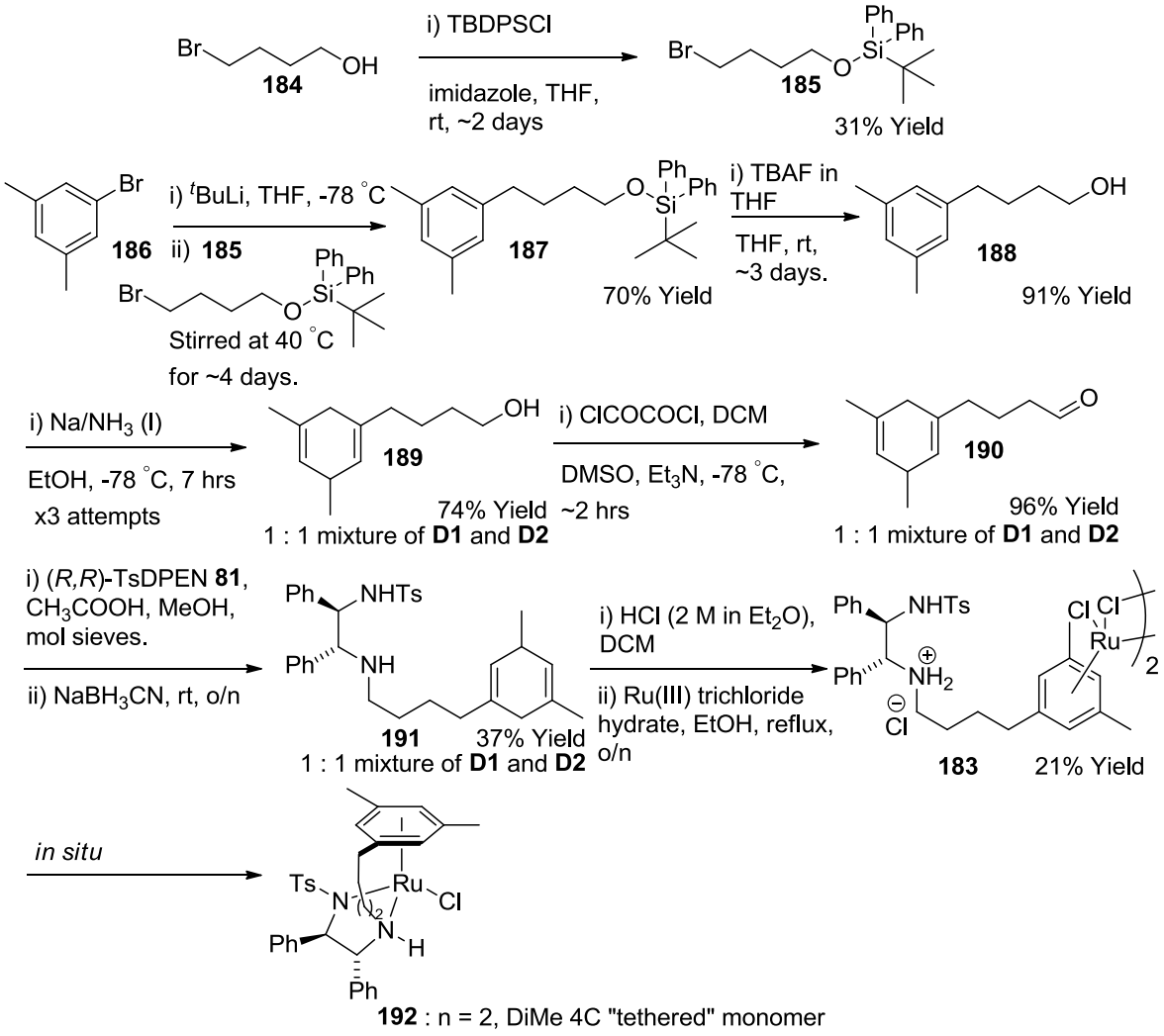


Figure 27. A graph to show conversion vs. time when carrying out ATH reduction of 2-methylquinoline **120a** to tetrahydroquinoline **120a'** using different catalysts at 60 °C.

2.1.5 Synthesis of catalyst 183 for the ATH reduction of quinolines.

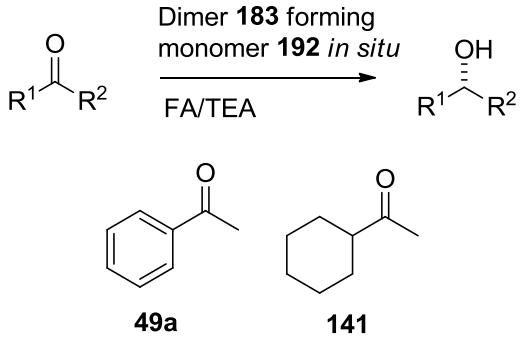
Dimer **183** was prepared successfully by firstly protecting 4-bromo-1-butanol **184** using *tert*-butyldiphenylsilyl chloride and imidazole in THF giving (4-bromobutoxy)(*tert*-butyl)diphenylsilane[26c] **185** with 31% conversion. The next step was a Br/Li exchange on 5-bromo-m-xylene **186** and reaction with **185** in THF giving *tert*-butyl(4-(3,5-dimethylphenyl)butoxy)diphenylsilane[26d] **187** with 70% yield, followed by deprotection of the silyl group using tetrabutylammonium fluoride in THF giving 4-(3,5-dimethylphenyl)butan-1-ol[26e] **188** in 91% conversion. Birch reduction was then carried out to reduce the aromatic ring on **188** with sodium and ethanol in liquid ammonia to form 4-(3,5-dimethylcyclohexa-1,4-dienyl)butan-1-ol **189** as a red oil in 74% yield. The second step was a Swern oxidation to oxidize **189** to 4-(3,5-dimethylcyclohexa-1,4-dienyl)butanal **190** using oxalyl chloride, dimethyl sulfoxide and triethylamine in DCM. Aldehyde **190** was afforded as a clear yellow oil in 96% yield. Thirdly, reductive amination was carried out in dry methanol using **190**, *R,R*-TsDPEN **81** and glacial acetic acid to form an imine as an intermediate, which then was reduced using sodium cyanoborohydride to give *N*-((1*R*,2*R*)-2-(4-(3,5-dimethylcyclohexa-1,4-dienyl)butylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **191** as a white solid in 37% yield. The final step was the complexation of **191** with via **191**.HCl salt formed from the reaction of **191** with 2M HCl in Et_2O in DCM, followed by the reaction of the salt with ruthenium(III) trichloride hydrate in refluxing ethanol overnight, forming **183** as a black solid in 21% yield. Dimer **183** then forms the monomer **192** *in situ* under ATH reaction conditions (Scheme 76).



Scheme 76. Synthesis of the DiMe 4C “tethered” dimer **183**.

2.1.6 ATH reduction of ketones using catalyst 183.

The reduction of substrate **120a** was not successful using catalyst **183**, so it was considered valuable to establish how well catalyst **183** reduces ketones in comparison to other catalysts, as 'tethered' complexes that have been made in the Wills group have given good results for the reduction of certain ketones as shown in Section 1.4.7 (Scheme 77, Table 41).



Scheme 77. ATH reduction of ketones **49a** and **141** giving alcohols **49a'** and **141'** respectively, using dimer **183**.

Ketone	Solvent	Temp (°C)	Catalyst	FA/TEA ratio	Time (hrs)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
49a	-	28	**(*R*,*R*)-183**	5:2	24	89	97 *R*
141	-	28	**(*R*,*R*)-183**	5:2	168	>99	74 *S*

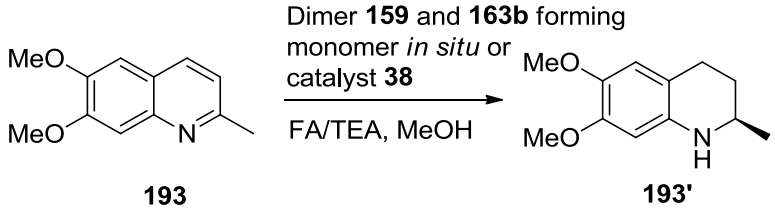
Table 41. ATH reduction of **49a** and **141** giving alcohols **49a'** and **141'** respectively, (Concentration of 1.62 M with respect to ketone, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **183** forming monomer **192** *in situ* (S/C = 400).

The reductions were successful and some good results were obtained. Acetophenone **49a** was reduced to the alcohol **49a'** giving 89% conversion and an impressive ee of 97% after 24 hrs, this reaction would possibly have reached >99% conversion if it was left to continue. Cyclohexylmethyl ketone **141** was reduced to the alcohol **141'** giving >99% conversion after 7 days with an ee of 74% (Table 41). Both the reductions are

comparable to the results obtained previously in the Wills' group for the reduction of ketones using untethered and 'tethered' complexes.

ATH reduction of 6, 7-dimethoxy-2-methylquinoline 193.

Synthesis of 6,7-dimethoxy-2-quinoline **193** follows the same procedure as **178**, via the Friedlander reaction, giving **193** in 76% yield.[26b] This reaction was a test to see whether having electron donating groups on the aromatic ring of the substrate has any effect on the conversion or enantioselectivity (Scheme 78, Table 42).



Scheme 78. ATH reduction of 6, 7-dimethoxy-2-methylquinoline **193** to **193'** using catalyst **38**, **159** and **163b**.

Imine	Solvent	Temp (°C)	Catalyst	FA/TEA ratio	Time (days)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
193	MeOH	28	**(*R*,*R*)-163b**	5:2	6	53	48 *R*
193	MeOH	28	**(*S*,*S*)-159**	5:2	4	23	48 *S*
193	MeOH	28	**(*R*,*R*)-38**	5:2	4	>5	- -

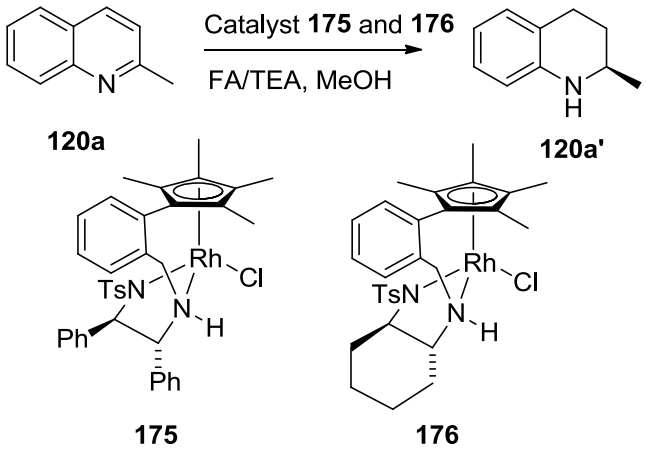
Table 42. ATH reduction of **193** to tetrahydroquinoline **193'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **159** and **163b** forming monomer *in situ* (S/C = 400) and catalyst **38** (S/C = 200).

The results obtained showed that having electron-donating groups on the aromatic ring of the quinoline slows the reaction down as quinoline **193** was reduced to the tetrahydroquinoline **193'** using catalyst **163b** with only 53% conversion after 6 days with an ee of 48%, and catalysts **159**/**38** were much slower as only 23% conversion was

obtained with an ee of 48% after 4 days for catalyst **159**, and only >5% conversion obtained using catalyst **38**, not enough conversion for determining the ee (Table 42).

2.1.7 ATH reduction of 2-methylquinoline; Using Rh "tethered" catalysts 175 and 176.

Reductions were carried out using 'tethered' Rh(III) **175** and analogue **176** catalyst for comparison with Ru(II) catalysts (Scheme 79, Table 43), as recently Xiao et al disclosed the use of Rh-based catalyst in aqueous solution (Section 1.4.6.5), and gave impressive results that required careful control of pH for full reduction to occur.



Scheme 79. ATH reduction of 2-methylquinoline **120a**, using catalyst **175** and **176**.

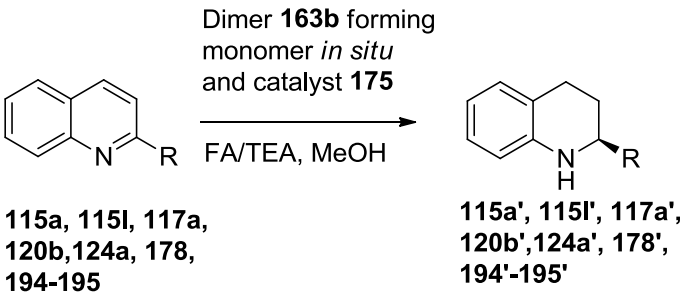
Imine	Solvent	Temp (°C)	Catalyst	FA/TEA ratio	Time (hrs)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
120a	MeOH	28	**(*R*,*R*)-175**	5:2	24	68	93 *R*
120a	MeOH	28	**(*R*,*R*)-176**	5:2	24	93	82 *R*

Table 43. ATH reduction of **120a** to tetrahydroquinoline **120a'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using catalyst **175** and **176** (S/C = 200).

ATH reduction using "tethered" Rh(III) catalysts proved be successful with catalyst **175** giving the best ee of 93%, and catalyst **176** giving the best conversion of 93% out of the two Rh(III) "tethered" catalyst's after 24 hours (Table 43).

2.1.8 ATH reduction of quinolines; using catalyst 163b and 175.

A series of quinoline substrates **115l**, **117a**, **120b**, **124a**, **194-195** (Figure 28) were synthesized [26b, 26f, 26g], from the initial reaction of 2-methylquinoline with ^{n}BuLi in dry THF at -78 °C followed by the addition of iodo/bromo containing starting materials. ATH reduction of quinolines **115l**, **117a**, **120b**, **124a**, **194-195** along with **115a** and **178** was carried out using the most active Ru(II) "tethered" catalyst **163b** and the most stereoselective Rh(II) "tethered" catalyst **175** tested (Scheme 80, Figure 28).



Scheme 80. ATH reduction of quinolines shown in Figure 28, using catalyst **163b** and **175**.

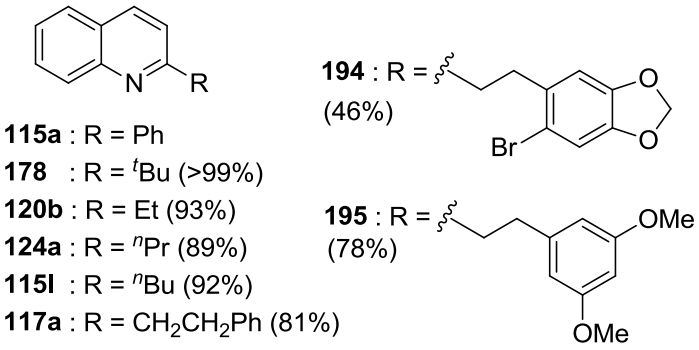


Figure 28. Substrates used for ATH reduction using catalyst **163b** and **175**.

Imine	Solvent	Temp (°C)	Catalyst	FA/TEA ratio	Time (hrs)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
120a	MeOH	28	**(*R*,*R*)-163b**	5:2	24	96	46 *R*
115a	MeOH	28	**(*R*,*R*)-163b**	5:2	168	68	73 *S*
178	MeOH	28	**(*R*,*R*)-163b**	5:2	48	57	0 -
120b	MeOH	28	**(*R*,*R*)-163b**	5:2	30	95	41 *R*
124a	MeOH	28	**(*R*,*R*)-163b**	5:2	144	94	42 *R*
115l	MeOH	28	**(*R*,*R*)-163b**	5:2	144	93	41 *R*
117a	MeOH	28	**(*R*,*R*)-163b**	5:2	48	90	50 *R*
194*	DCM	28	**(*R*,*R*)-163b**	5:2	48	86	47 *R*
195	MeOH	28	**(*R*,*R*)-163b**	5:2	48	93	67 *R*

Table 44. ATH reduction of quinolines to tetrahydroquinolines (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **163b** forming monomer *in situ* (S/C = 400). *Substrate **194** did not dissolve in MeOH, EtOH, ACN and IPA.

The results show that the reductions to tetrahydroquinoline for all the substrates were carried out successfully and with high conversions, with substrate **120a** giving the highest conversion of 96% and substrate **178** giving the lowest conversion of 57%. The ee's obtained for the tetrahydroquinolines were not so high, with substrate **115a** giving the highest ee of 73% (Table 44).

As "tethered" Rh(III) catalysts showed good activity and great stereoselectivity for the reduction of quinolines, it was further employed for the reduction of a series of quinolines (Scheme 80, Figure 28).

Imine	Solvent	Temp (°C)	Catalyst	FA/TEA ratio	Time (hrs)	Conv. (%)**	ee (%)***/ Config. (*R*/*S*)
120a	MeOH	28	**(*R*,*R*)-175**	5:2	24	68 (85)	93 *R*
115a	MeOH	28	**(*R*,*R*)- 175**	5:2	48	30 (35)	86 *S*
178	MeOH	28	**(*R*,*R*)- 175**	5:2	48	16 (43)	0 -
120b	MeOH	28	**(*R*,*R*)-175**	5:2	48	67 (76)	91 *R*
124a	MeOH	28	**(*R*,*R*)-175**	5:2	48	65 (73)	90 *R*
115l	MeOH	28	**(*R*,*R*)-175**	5:2	48	64 (76)	92 *R*
117a	MeOH	28	**(*R*,*R*)-175**	5:2	48	57 (65)	93 *R*

194*	DCM	28	**(*R,R*)-175**	5:2	48	30 (29)	81 *R*
195	MeOH	28	**(*R,R*)-175**	5:2	48	58 (69)	94 *R*

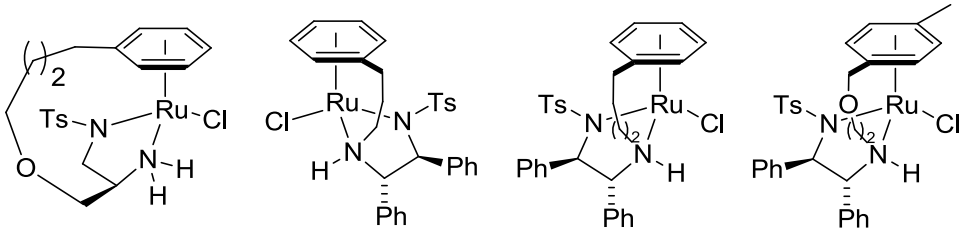
Table 45. ATH reduction of quinolines to tetrahydroquinolines (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using catalyst **175** (S/C = 200). *Substrate **194** did not dissolve in MeOH, EtOH, ACN and IPA. **Figures in parenthesis indicate conversion after 2 days using 2 mol% catalyst. ***ee of product of 0.5 mol% catalyst loading reaction.

The results show that the reductions of quinolines to tetrahydroquinolines for all the substrates were carried out successfully and with high ee's, with substrate **195** giving the highest ee of 94% (Table 45). As the reactions were not going to completion the catalyst loading was changed to 2 mol%** from 0.5 mol%, and this gave an increase in % conversion for all the substrates, with the highest conversion given by substrate **120a** of 85%, but the reductions still did not go to completion.

In summary, it has now been demonstrated that Ru(II) and Rh(II) complexes are effective catalysts for the ATH reduction of substituted quinolines, which are generally regarded as challenging substrates for this application. Also as seen for ketone reductions (Section 1.4.7), the increased reactivity of "tethered" complexes over the untethered catalysts appears to be key to their capacity to work as effective catalysts in this application.

2.2 Synthesis of ether-linked "tethered" catalyst for the ATH reduction of ketones.

The objective of this project was the synthesis of an ether-linked "tethered" catalyst. Wills and co-workers had previously reported the synthesis of a stereochemically well defined catalyst **173b** that controlled the configuration of the metal with the use of a ether-linked "tether", showing good activity but lacked elements which affect the enantioselectivity of ketone reductions (Section 1.4.7). The ether-linked "tethered" catalyst **207** represented an interesting target to synthesize and includes all the necessary features for making it a desirable catalyst in terms of its promise for rate and enantioselectivity for ketone reductions. The "tether" is linked to the "basic" amine which has proved to be vital for achieving high activity, and the "tether" chain has 4 substituents (-$CH_2CH_2OCH_2$-), as the 4C alkyl chain "tethered" catalyst **165** having 4 substituents had proved to be the most active catalyst among the rest of its class (**160** and **165**, Figure 29) (Section 1.4.7). TsDPEN **81**, with matching stereocentres and a *trans* orientation of the phenyl groups was also employed for the synthesis of this catalyst (Section 1.4.5), which in effect will help enhance the rate and enantioselectivity of an ATH reaction.

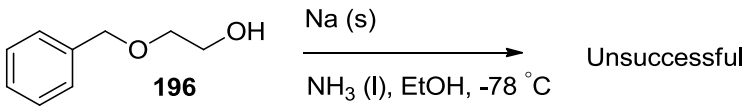


(*R*)-**173b** (*S,S*)-**160** (*R,R*)-**165** (*R,R*)-**207**

Figure 29. Ru(II) "tethered" catalyst.

2.2.1 Synthesis of the ether-linked "tethered" catalyst 207.

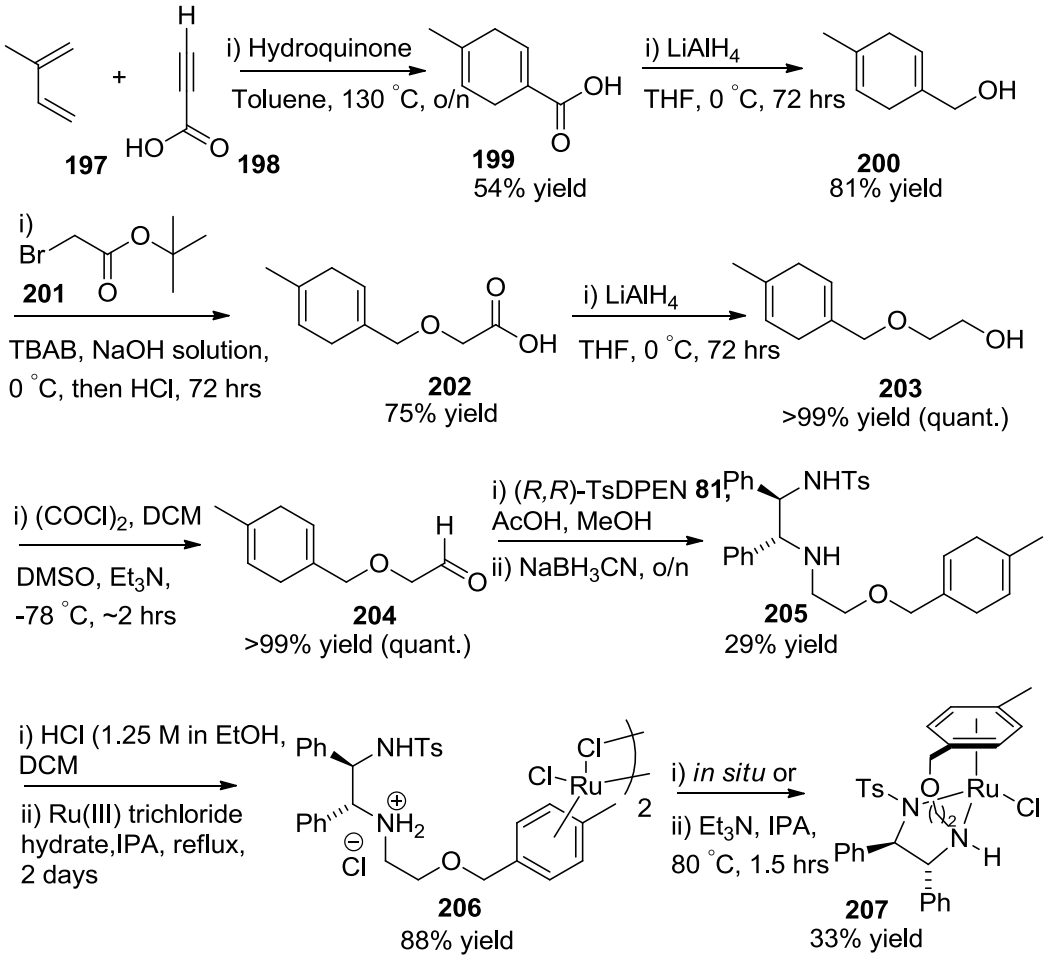
The initial step in the route for synthesizing **207**, using Birch reduction on 2-(benzyloxy)ethanol **196** was unsuccessful as it resulted in the cleavage of the ether (Scheme 81).



Scheme 81. Attempted Birch reduction on 2-(benzyloxy)ethanol **196**.

With the Birch reduction step being problematic, an alternative approach was devised to gain access to the 1, 4-cyclohexadienyl moiety. In the synthesis of catalyst **207** (Scheme 81), the Diels-Alder cycloaddition was employed to attain the 1,4-cyclohexadienyl containing compound. Cycloaddition of isoprene **197** with propiolic acid **198** in THF at reflux temperature furnished 4-methylcyclohexa-1,4-dienecarboxylic acid **199**[27a] in 54% yield as a white solid, which then was reduced using $LiAlH_4$ in THF giving (4-methylcyclohexa-1,4-dienyl)methanol **200**[17j] in 81% yield as a colourless oil. The coupling of **200** with *tert*-butylbromoacetate **201** in NaOH solution and using TBAB led to the formation of 2-((4-methylcyclohexa-1,4-dienyl)methoxy)acetic acid **202**[27b] in 75% yield as a light yellow solid. Compound **202** was reduced with $LiAlH_4$ in THF giving 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)ethanol **203**[17j] in >99% yield (quant.) as a yellow oil, and oxidised via Swern oxidation to form 2-((4-methylcyclohexa-1,4-dienyl)methoxy)acetaldehyde **204**[20a] in >99% yield (quant.) as an orange oil. Reductive amination was carried out in methanol using **204**, *R*,*R*-TsDPEN **81**[27c] and glacial acetic acid to form an imine as an intermediate, which then was reduced to give 4-methyl-*N*-((1*R*,2*R*)-2-(2-((4-methylcyclohexa-1,4-dienyl)methoxy)ethylamino)-1,2-diphenylethyl)benzenesulfonamide **205**[20a] as a white

solid in 29% yield using sodium cyanoborohydride. The final step was the complexation of **205** with ruthenium(III) trichloride hydrate in refluxing IPA, after formation of **205**.HCl using HCl (1.25 M in EtOH) in anhydrous DCM, giving **206**[20a] as a black solid in 88% yield (if carried out in ethanol gives a low yield of 14%). The dimer **206** could be directly used in ATH reactions, as it forms **207** under reaction conditions, in common with related complexes that are converted from their dimer forms to monomer *in situ*. The formation of monomer **207**[20a] using Et_3N in IPA at 80 °C, was successful as confirmed by mass spectroscopy, and ^1H NMR spectroscopic analysis of the crude product. The isolation of the pure complex **207**, was however challenging in contrast to the alkyl chain complexes which were universally stable to purification by chromatography. Decomposed material was obtained in the attempt to purify **207**. For this reason monomer **207** was either used in crude form, or more conveniently, the dimeric precursor **206** was employed directly in ATH reactions.

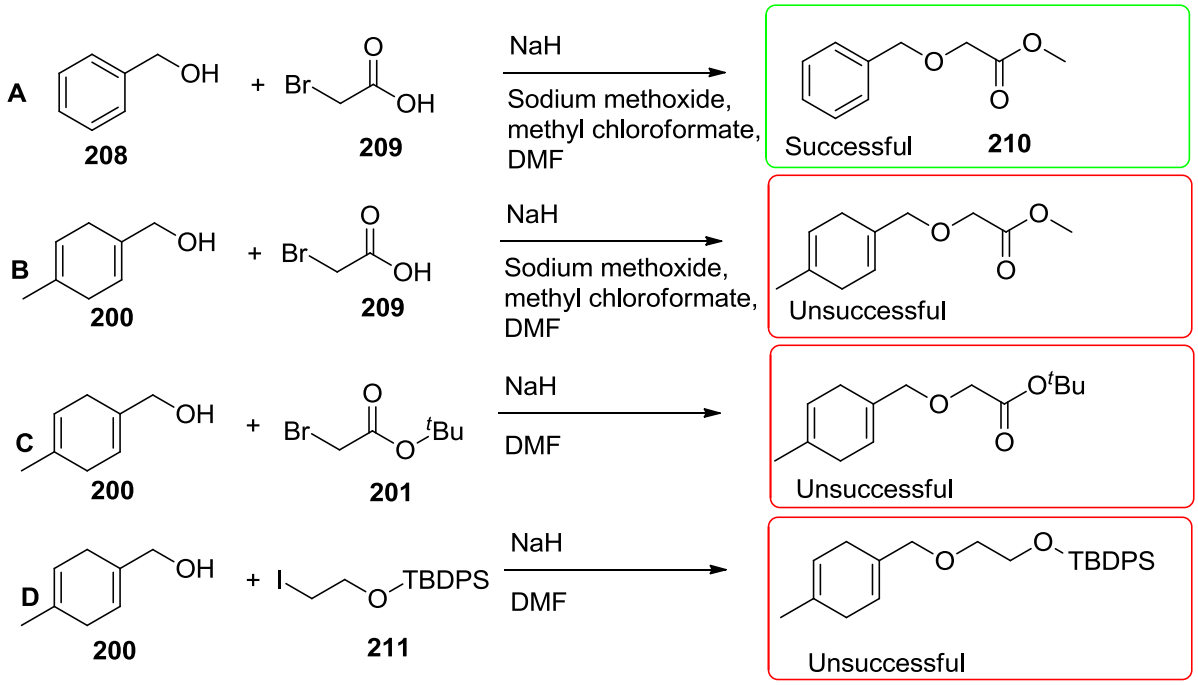


Scheme 82. Synthesis of ether-linked "tethered" catalyst **207**.

Problems encountered during the synthesis of 207.

The formation of **202** was successful after **200** was coupled with *tert*-butylbromoacetate **201** in NaOH solution and using TBAB. This method was employed as the coupling of **200** using NaH proved to be unsuccessful. A test reaction was first carried out (A, Scheme 83) in which benzyl alcohol **208** was coupled to bromoacetic acid **209** using NaH, with the addition of **208**, **209** followed by sodium methoxide and methylchloroformate in to a solution of NaH in DMF were carried out at 0 °C, then allowed to stir at rt overnight resulting in a successful formation of **210**.[27d] The reaction was repeated using **200**, and proved to be unsuccessful (B, Scheme 83), also failing when using **201** (C, Scheme 83), *tert*-butyl(2-iodoethoxy)diphenylsilane **211**[26c]

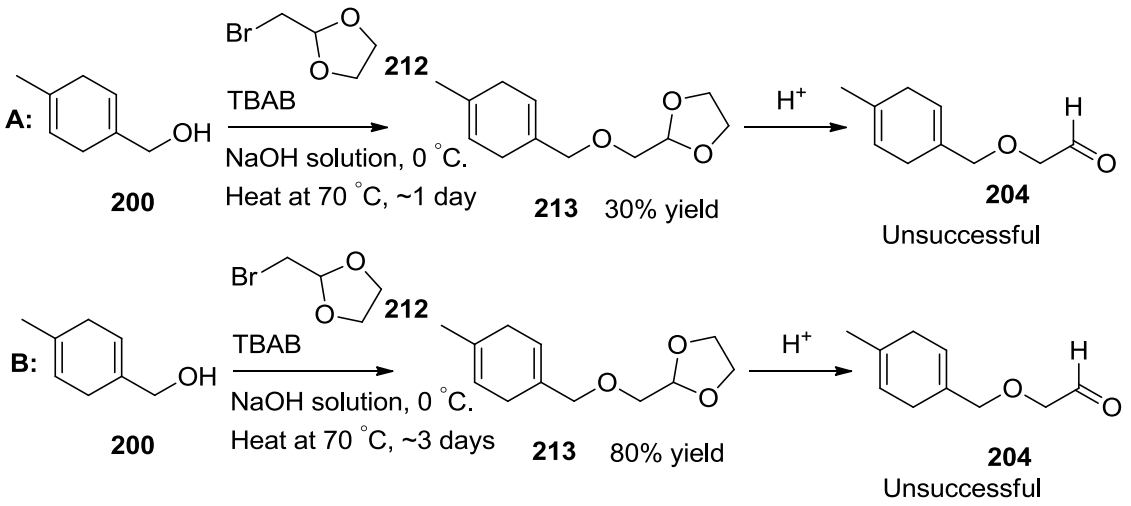
(prepared by the drop wise addition of *tert*-butyl-chlorodiphenylsilane to a solution of 2-iodoethanol and imidazole dissolved in THF) (D, Scheme 83), and when experimenting with temperature.



Scheme 83. Failed coupling attempts using NaH.

Further work on the synthesis of the ether-linked "tethered" catalyst.

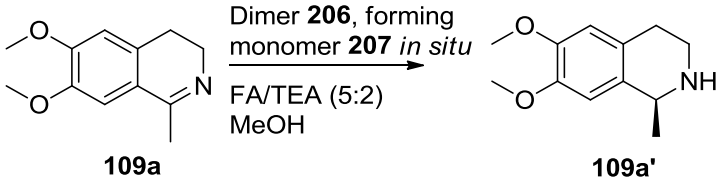
In an attempt to form aldehyde **204** in a one-pot reaction, alcohol **200** was reacted with 2-bromomethyl-1,3-dioxolone **212** and TBAB in NaOH solution at 0 °C. Stirring the reaction at 70 °C for 1 day had given **213** with 30% yield, and leaving the reaction for 3 days had further increased the yield to 80%. The addition of 1 M HCl and 5 M HCl to **213** had showed changes in the ^{1}H NMR, but the product had decomposed after the addition of conc. HCl. Further investigations need to be carried out for this step as removing the reduction step for the synthesis of the ester-linked "tethered" catalyst, could be highly beneficial when synthesized on a large scale in industry (Scheme 84)



Scheme 84. Synthesis of the aldehyde **204** in a one-pot reaction.

2.2.2 Reduction of imine with ether-linked "tethered" dimer 206.

After the successful formation of catalyst **206**, it was worth carrying out an ATH reduction on 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **109a** to see how active and stereoselective the catalyst is for this substrate (Scheme 85, Table 46).



Scheme 85. ATH reduction of **109a** using catalyst **206**.

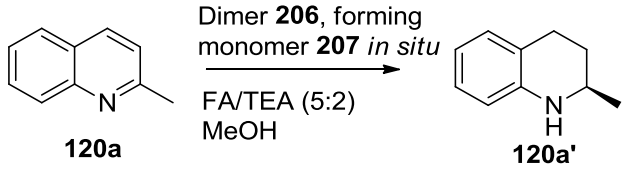
Imine	Catalyst	Temp (°C)	Time (days)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
109a	**(*R*,*R*)-206**	28	4	100	87 *S*

Table 46. ATH reduction of **109a** to tetrahydroisoquinoline **109a'** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. azeotropic mixture used); Using dimer **206** forming monomer **207** *in situ* (S/C = 400).

The results showed that catalyst **206** was successful for the reduction of **109a**, giving 6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **109a'** in 90% conv., and a respectable 87% ee (*S*) after 4 days (Table 46).

2.2.3 Reduction of quinoline with ether-linked "tethered" dimer 206.

The next task was to carry out the ATH reduction with catalyst **206** on 2-methylquinoline **120a** (Scheme 86, Table 47).



Scheme 86. ATH reduction of 2-methylquinoline **120a** using catalyst **206**.

Imine	Catalyst	Temp (°C)	Time (days)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
120a	**(*R*,*R*)-206**	28	6	65	61 *R*

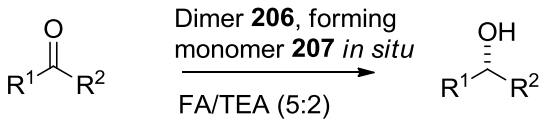
Table 47. ATH reduction of 2-methylquinoline **120a** to tetrahydroquinoline **120a'** (Concentration of 0.45 M with respect to quinoline, non-dropwise i.e. azeotropic mixture used); Using dimer **206** forming monomer **207** *in situ* (S/C = 400).

The reduction of **120a** was successful giving the 2-methyl-1,2,3,4-tetrahydroquinoline **120a'** in 65% conv., 61% ee (*R*) (Table 47). After 24 hrs, the conversion was 57%, and after 6 days it was 65%. The ee obtained for the reduction of **120a** is the highest to have been achieved with any Ru(II) "tethered" catalyst.

2.2.4 Reduction of ketones with ether-linked "tethered" dimer 206.

ATH reductions have now been tested out on an imine and a quinoline with catalyst **206**. The next step was to focus on the ATH reduction of ketones to alcohols with catalyst **206** (Scheme 87). The majority of substrates tested were reduced successfully,

giving the alcohols with excellent conversions (in the best cases >99%) and enantioselectivities in some cases of >99%). ATH reduction of acetophenone derivatives containing para- **49c** and meta-chloro substituents **49b**, and bicyclic derivatives such as α-tetralone **214** and 4-chromanone **215** were reduced in similar conversions and enantioselectivities to acetophenone itself. The ortho-chloro substituted acetophenone derivative **216** however gave a reduced ee of 87%, which has been observed previously for reduction of this substrate with a similar catalyst (Scheme 87, Figure 30, Table 48).[17e, 17i, 18a, 20a, 21b, 25a, 25c-e, 25i, 27e-27h]



Scheme 87. ATH reduction of ketones, using catalyst **206**.

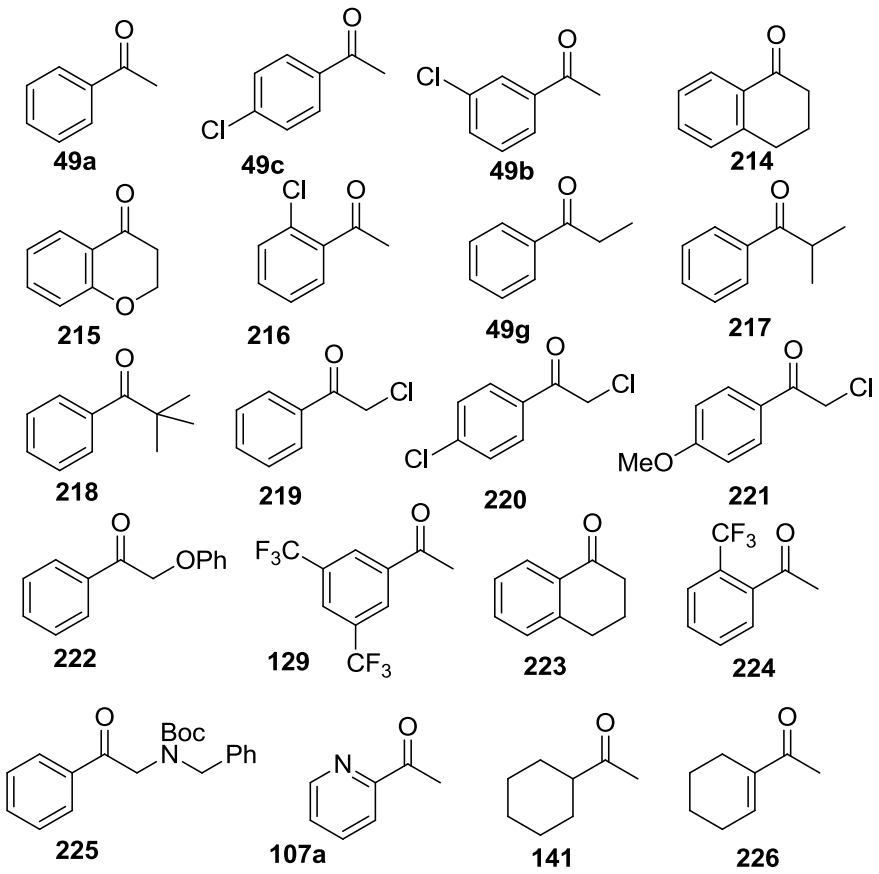


Figure 30. ATH reduction of a series of ketones.

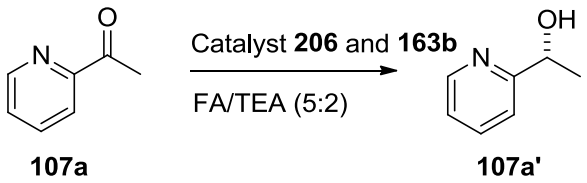
Ketones	Catalyst	Temp (°C)	Time (days)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
49a	**(*R*,*R*)-206**	28	o/n	>99	99 *R*
49c	**(*R*,*R*)-206**	28	o/n	>99	96 *R*
49b	**(*R*,*R*)-206**	28	2	>99	94 *R*
214	**(*R*,*R*)-206**	28	2	>99	>99 *R*
215	**(*R*,*R*)-206**	28	o/n	>99	>99 *R*
216	**(*R*,*R*)-206**	28	2	100	87 *R*
49g	**(*R*,*R*)-206**	28	2	>99	>99 *R*
217	**(*R*,*R*)-206**	28	2	11	27 *R*
218	**(*R*,*R*)-206**	28	2	6	14 *R*
219	**(*R*,*R*)-206**	28	o/n	>99	98 *S*
220	**(*R*,*R*)-206**	28	o/n	>99	96 *S*
221	**(*R*,*R*)-206**	28	o/n	>99	97 *S*
222	**(*R*,*R*)-206**	28	o/n	>99	95 *S*
129	**(*R*,*R*)-206**	28	o/n	>99	60 *R*
224	**(*R*,*R*)-206**	28	4	22	17 *R*
225	**(*R*,*R*)-206**	28	10	99	>99 *S*
107a	**(*R*,*R*)-206**	28	4	0	0 -
141	**(*R*,*R*)-206**	28	4	>99	0 -
226	**(*R*,*R*)-206**	28	13	>99	71 *R*

Table 48. ATH reduction of ketones to alcohols (Concentration of 1.62 M with respect to ketone, non-dropwise i.e. azeotropic mixture used); Using dimer **206** forming monomer **207** *in situ* (S/C = 400).

Propiophenone **49g** was reduced successfully, giving **49g'** in excellent conversion, and ee. Increasing the size of the alkyl group to isopropyl and *tert*-butyl however resulted in an extreme drop in activity and enantioselectivity, giving **217'** and **218'** in poor conv., and ee. This is dissimilar to the alkyl "tethered" complex **160**, which is more versatile in this respect. Excellent results were obtained for α-chloroacetophenones **219-221**, which lead to alcohols **219'-221'**, and are useful intermediates for the formation of epoxides and other chiral building blocks. Related substrates **222** and **225** that contain an O and N heteroatom on the alkyl substituent side can also be reduced successfully in excellent conversions and ee's. Introducing electron-withdrawing trifluoromethyl groups in to the

substrate appeared to be detrimental to the enantioselectivity, as **129'** was formed in just 60% ee whilst the ortho-substituted **224** was reduced in just 22% conversion and 17% ee. An unexpected result was obtained for 2-acetylpyridine **107a**, which was not reduced at all by catalyst **206** under the reaction conditions used. The reduction of **223** was unsuccessful as the starting material was decomposing over time.

The reduction of 2-acetylpyridine **107a** was carried out using catalyst **165**, with identical conditions to when catalyst **206** was employed previously in the reaction. Reduction of **107a** was successful giving **107a'** in >99% conv., and 88% ee, which is in agreement with another alkyl-"tethered" catalyst **160** previously used for this reduction (Scheme 88, Table 49).[20a]

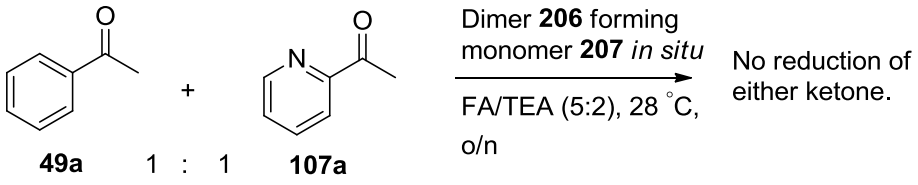


Scheme 88. ATH reduction of **107a**, using catalyst **206** and **163b**.

Ketone	Catalyst	Temp (°C)	Time (days)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
107a	**(*R*,*R*)-206**	28	4	0	0 -
107a	**(*R*,*R*)-163b**	28	o/n	>99	88 *R*

Table 49. ATH reduction of **107a** to **107a'** (Concentration of 1.62 M with respect to ketone, non-dropwise i.e. azeotropic mixture used); Using dimer **206** forming monomer **207** *in situ* also dimer **163b** (forming **165**) (S/C = 400).

At this stage it was worth investigating to see whether or not the substrate was inhibiting the reaction. To test this, the reduction of a 1 : 1 mixture of 2-acetylpyridine **107a** and acetophenone **49a** was attempted with catalyst **206** (Scheme 89).



Scheme 89. ATH reduction of a 1 : 1 mixture of **107a** and **49a**, using catalyst **206** (S/C = 400).

The results showed that neither of the ketones were reduced (Scheme 89), suggesting that 2-acetylpyridine **107a** is inhibiting the catalysis of the reaction, by a mechanism which is presently unclear but may involve an interaction of the protonated N atom of the pyridine with the oxygen atom on the "tether". This would stabilise the complex between the catalyst and both the substrate and product to the point where product is not released (Figure 31), hence preventing catalyst turnover as reflected in the competition experiment. This additional interaction is not available to **165** and **160**, and so is not inhibited by this substrate.

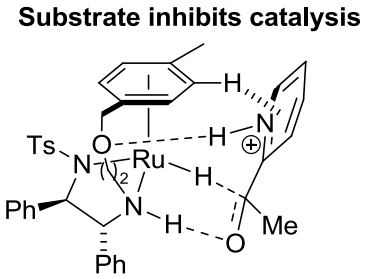


Figure 31. **107a** inhibits catalysis due to an additional interaction of the protonated pyridine with the O atom on the "tether" in catalyst **207** (formed from dimer **206**).

The reduction of cyclohexylmethyl ketone **141**, which is a useful test ketone for dialkyl substrates, was catalysed by **206** with full conversion however racemic alcohol **141'** was obtained. This is in contrast to the 69% ee achieved for this substrate using alkyl-"tethered" catalyst **160** (Section 1.4.7). The reduction of a structurally similar but unsaturated ketone **226**, in contrast, was achieved in full conversion in 71% ee but after

13 days of reaction. The reduction to form **226'** could be directed by a similar CH/π interaction as for acetophenone derivatives (Figure 32).

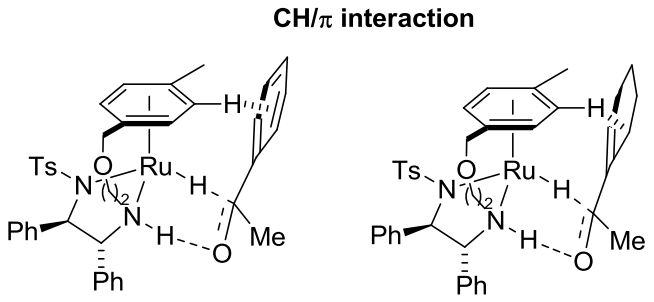
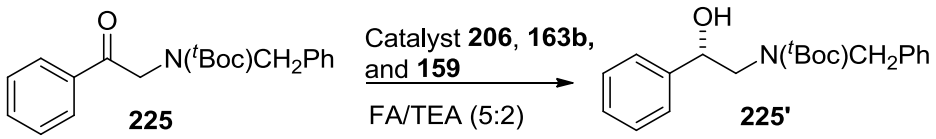


Figure 32. CH/ π interaction between η^6-arene ring of the catalyst and the aromatic ring of the substrate.

2.2.5 Comparative studies.

A comparison in activity and selectivity using catalyst **206** (forming **207**), **163b** (forming **165**) and **159** (forming **160**) was carried out for the reduction of **225**, which showed that catalyst **206**, **163b** and **159** all demonstrated similar activity and reactivity for the reduction of **225** (Scheme 90, Table 50).



Scheme 90. ATH reduction of **225**, using catalyst **206**, **163b** and **159**.

Ketone	Catalyst	Temp (°C)	Time (days)	Conversion (%)	ee (%)/ Config. (*R*/*S*)
35	**(*R*,*R*)-206**	28	10	>99	>99 *S*
35	**(*R*,*R*)-163b**	28	8	>99	>99 *S*
35	**(*S*,*S*)-159**	28	10	>99	>99 *R*

Table 50. ATH reduction of **225** to **225'** (Concentration of 1.62 M with respect to ketone, non-dropwise i.e. azeotropic mixture used); Using dimer **206** forming monomer **207** *in situ* and dimers also for **163b** (forming **165**) and **159** (forming **160**) (S/C = 400).

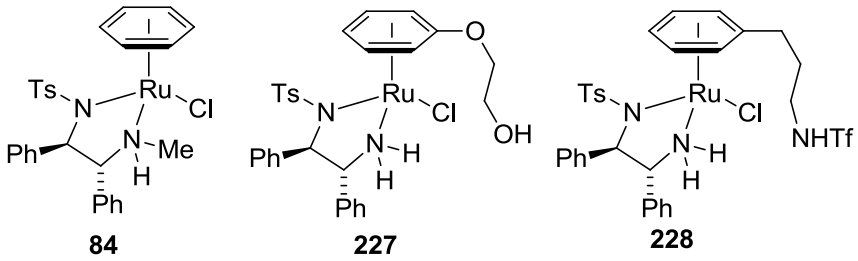
In conclusion, the results suggest that the interaction of certain ketones with the ether-linked "tethered" catalyst **206** (forming monomer **207** *in situ*) is somewhat different to their interaction with the alkyl-chain version such as catalysts **165** and **160**. The sense of reduction in each case however shows that the catalyst **206** operates through a mechanism which is analogous to that of complex **165** and **160**. This involves a key stabilising CH/π interaction between η^6-arene ring of the catalyst and the aromatic ring of the substrate.

During the preparation of this thesis, Ikariya et al, published[27i] a synthesis of catalyst **207** via a route different to that in this thesis and tested it in the ATH of a range of ketones distinct from the selection in this thesis. The ^{1}H NMR spectroscopic data of the monomeric complex obtained by Ikariya matched that of the crude material obtained from dimer **206** in this project.

2.3 *N*-Alkylated TsDPEN ligands for ATH reductions.

As now it was established that ether-linked "tethered" catalysts were capable of reducing ketones, it was worth investigating the effects of having an ether- or alcohol-containing chain on the "basic" nitrogen atom without it being "tethered" to the η^6-arene ring. This transformation can provide means for attaching the catalyst to a hetereogeneous support. As mentioned in Section 1.4.3.2, catalyst **84** can be monosubstituted without the loss of catalytic activity or selectivity, provided that the subsituent is a linear alkyl group, as branched or sterically-hindered substituents cause a sharp reduction of activity. In contrast to extensive studies on the primary amine-containing TsDPEN, a relatively small number of successful applications of *N*-alkylated TsDPEN-derived catalysts have been reported.[28a-f] These include applications to C=C reduction[28a] and use in reversible formate decarboxylation studies.[28b,28c] In addition, the

application of *N*'-alkylated derivatives of *N*-tosyl-1,2-diaminocyclohexane (TsDAC) to ketone and imine ATH has been reported.[28d, 28e] Although oxygen-containing chains has not been previously studied, one report on the successful use in ATH of a TsDPEN ligand containing a PEG chain has been published.[28f] There appear to be no published studies on the use of *N*-hydroxy-functionalised substituents, which have the potential to interact with the ruthenium atom in an analogous manner to a previously-reported catalyst **227** (Figure 33) containing a 2-hydroxyethyl group on the η^6-arene ring.[28g] In other related examples published by Ikariya, and NHTf group at the end of a 3-carbon chain from the η^6-arene ring, i.e. in **228** (Figure 33), was reported to give improved results in the asymmetric hydrogenation during the catalytic cycle.[28h, 28i]

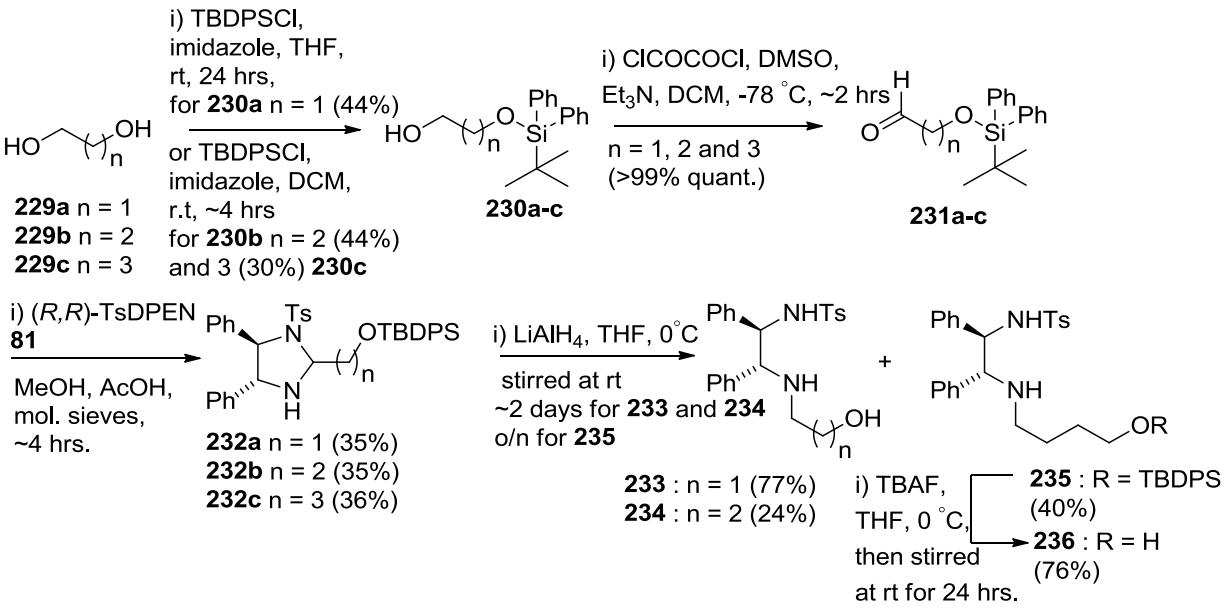


84 **227** **228**

Figure 33. Previously reported functionalized Ru(II) catalysts.

2.3.1 Preparing *N*-alkylated ligands.

N-Alkylated ligands were prepared by via the route shown in Scheme 91. Diols **229a-c** were first of all mono protected with the use of *tert*-butyldiphenylchlorosilane (TBDPSCl) and imidazole in THF at rt.[26c] In order to prevent diprotection, solvent for n =2 and n =3 in **229b-c** was replaced with DCM,[28j] having a saturated solution (protecting group in excess). The monosilylated diols **230a-c** were then oxidized to give the aldehydes **231a-c** via Swern oxidation,[29a] followed by aminal formation **232a-c** with (*R*,*R*)-TsDPEN **81** using glacial acetic acid in dry methanol (Scheme 91).[29a]



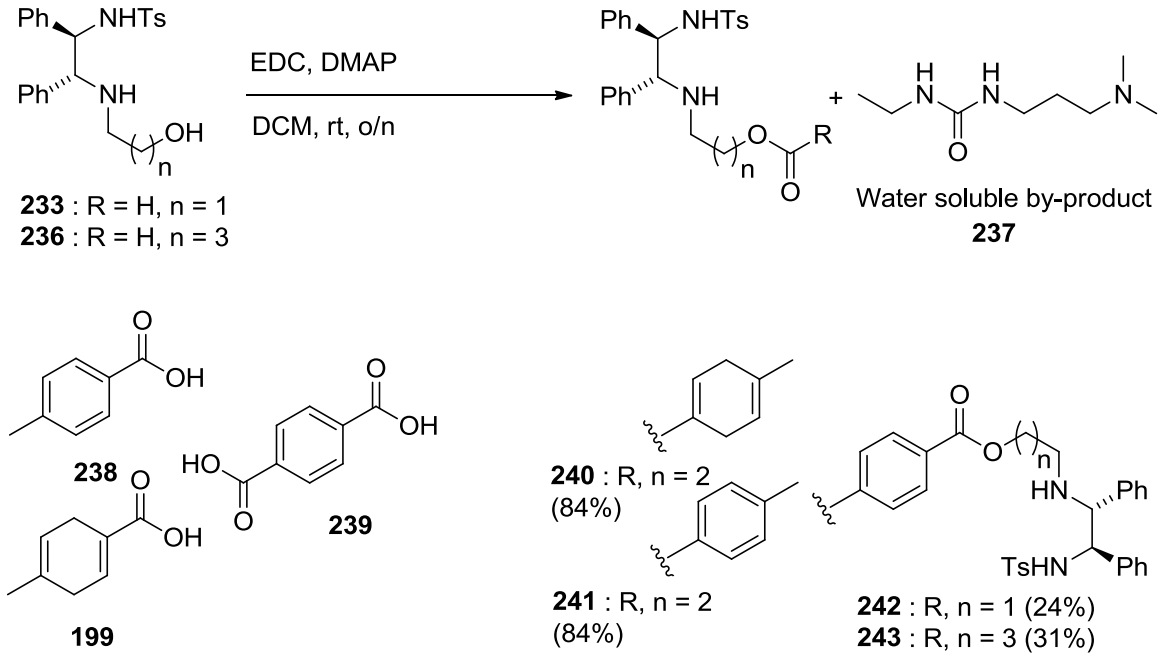
Scheme 91. Synthesis of hydroxy *N*-alkylated ligands.

Reduction of the aminals **232a-c** using $LiAlH_4$, resulted in the formation of **233**[29a] and **234** through aminal reduction coupled with desilylation under the same conditions. Ligands **235** and **236** both containing a linear 4C groups, were prepared by an analogous sequence to **233-234**, with the difference that the $LiAlH_4$ treatment at the end of the sequence did not simultaneously remove the silyl group, i.e. the product was silyl ether **235**. The silyl group was however removed in a subsequent step using TBAF to furnish **236**.[29a]

2.3.2 Ester-containing ligands.

The ester-containing ligands **240-241** were prepared by reaction of *N*-hydroxyethylTsDPEN **233** and **236** with acids **238** and **199**, using a combination of DCC and DMAP as the coupling reagent in DCM. DCC was however replaced with ethyl-(*N*',*N*'-dimethylamino)propylcarbodiimide hydrochloride (EDC), as this carbodiimide reagent and its urea by-product **237** are water soluble, so the by-product and any excess reagent are removed by aqueous extraction. Dicyclohexylurea, the by-product formed from DCC is nearly insoluble in most organic solvents and precipitates

from the reaction mixture as the reaction progresses (Scheme 92).[29b] The coupling of **233**, with propiolic acid **198** was unsuccessful, with both starting materials obtained unreacted.



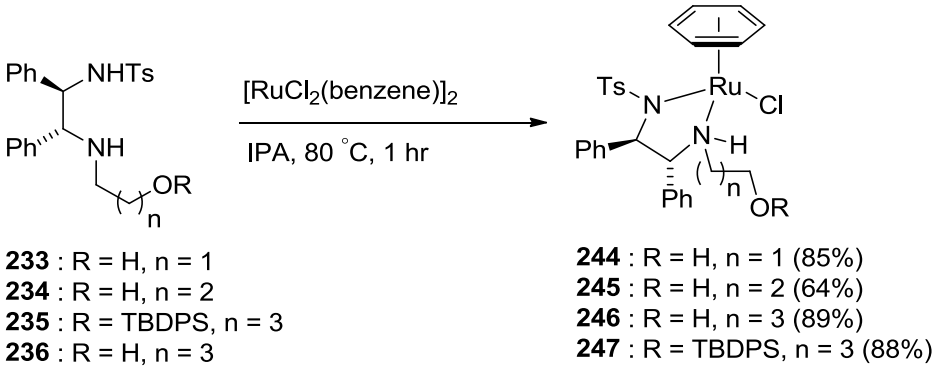
Scheme 92. Synthesis of ester-linked *N*-alkylated ligands.

Dimeric ligands **242** and **243** were prepared by an analogous process, starting from the 1,4-dicarboxylic acid **239**. The initial attempts to form ester-linked *N*-alkylated ligands had failed considerably with the reaction of alcohol **233** to the carboxylic acid **199** transformed in to acid chloride in DCM.[29c] Also with another alcohol and acid coupling method using methanesulfonic acid, aluminium oxide, sodium bicarbonate in ethyl acetate.[29d]

2.3.3 *N*-Alkylated Ru(II) complex formation.

A number of isolated complexes **244-247** were also prepared by the reaction of **233-236** with $[RuCl_2(benzene)]_2$ in IPA at 80 °C for 1 hr (noting that the use of η^6-benzene gives

significantly improved results over other η^6-arenes when *N*-alkylated TsDPENs are employed in ATH reactions) (Scheme 93).[17j]

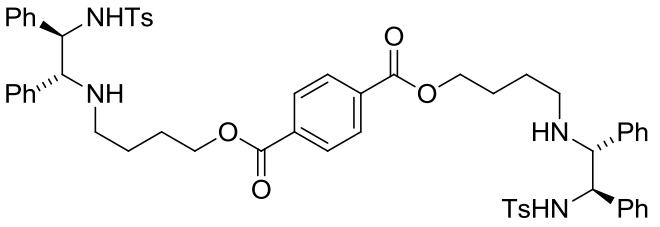


233 : R = H, n = 1
234 : R = H, n = 2
235 : R = TBDPS, n = 3
236 : R = H, n = 3

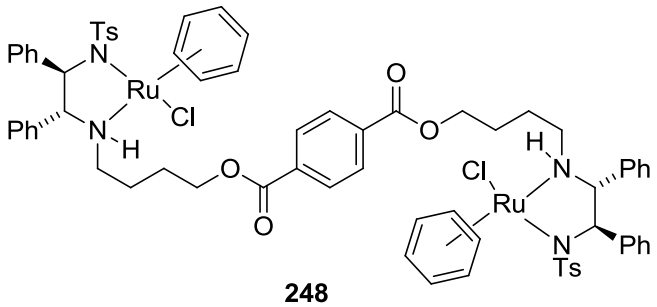
244 : R = H, n = 1 (85%)
245 : R = H, n = 2 (64%)
246 : R = H, n = 3 (89%)
247 : R = TBDPS, n = 3 (88%)

Scheme 93. Synthesis of *N*-alkylated complexes **244-247**.

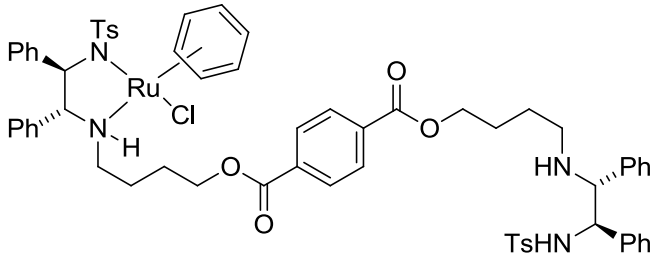
Complexation of ester-linked ligands **240, 242** and **243** proved problematic as long reaction times were required, or else starting ligand was still present. However, after long reaction times the products were formed in small quantities and were quite unstable, along with large quantities of decomposed material. The complexation of dimeric ligand **243**, gave a mixture of two products **248** + **249** as suggested by ^{1}H NMR and LR MS, along with the starting unreacted ligand **243** (Figure 34).



243



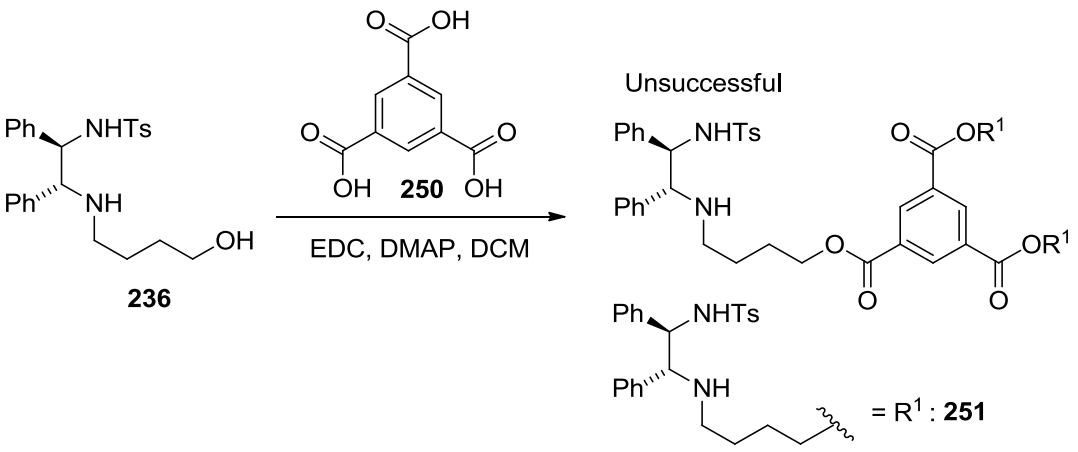
248



249

Figure 34. Products formed after complexation of ligand **243** with $[RuCl_2(benzene)]_2$.

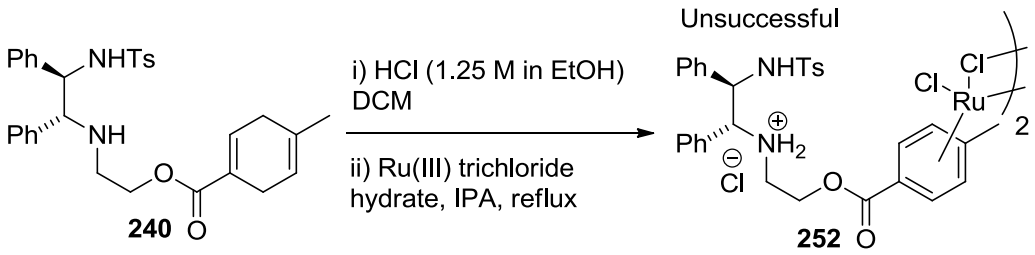
An attempt to form a "trimeric" ligand **251** was also carried out using acid **250**, proving to be unsuccessful, as an unknown product that couldn't be identified with very broad ^1H NMR peaks was formed (Scheme 94). Further work was not conducted using the ester-linked ligands.



Scheme 94. Attempted synthesis of "trimeric" ligand **251** using **236** and **250** had failed.

Attempted formation of Ester-linked "tethered" catalyst 252 (dimer).

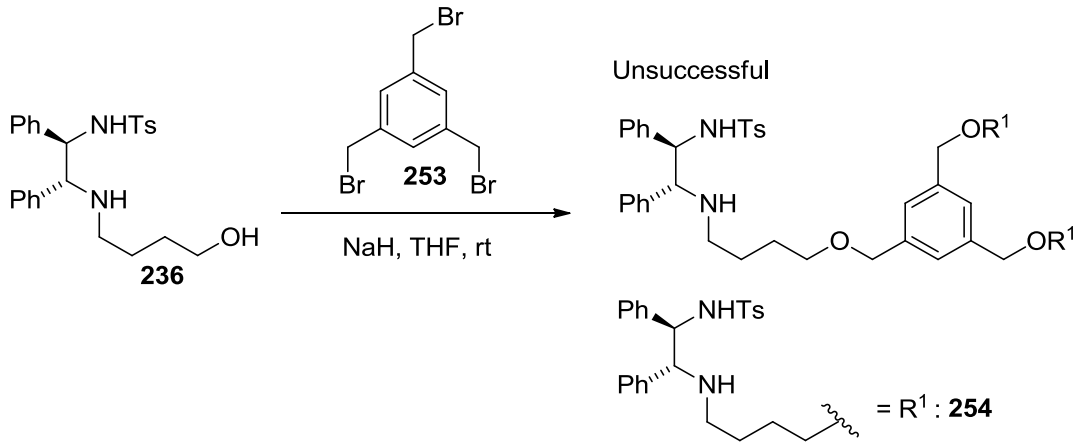
As attempts to form the ester with a 1,4-cyclohexadienyl moiety were successful, it was considered worth testing whether an ester-linked "tethered" catalyst could be formed. Complexation using **240**, first forming the ligand salt **240**.HCl using HCl in DCM, followed by refluxing of the salt in IPA gave a black solid product **252**. Product analysis using ^{1}H NMR, LR MS and HR MS showed no signs of product formation. It was still however tested for the ATH reduction of acetophenone **49a** and cyclohexylmethyl ketone **141**, but no conversion was observed and no presence of the monomeric catalyst was seen by LR MS. Monomer formation was also attempted separately by heating **252** with Et_3N in IPA at 80 °C, but no product was formed as confirmed by ^{1}H NMR and LR MS (Scheme 95).



Scheme 95. Attempted formation of ester-linked "tether" dimer **252** had failed.

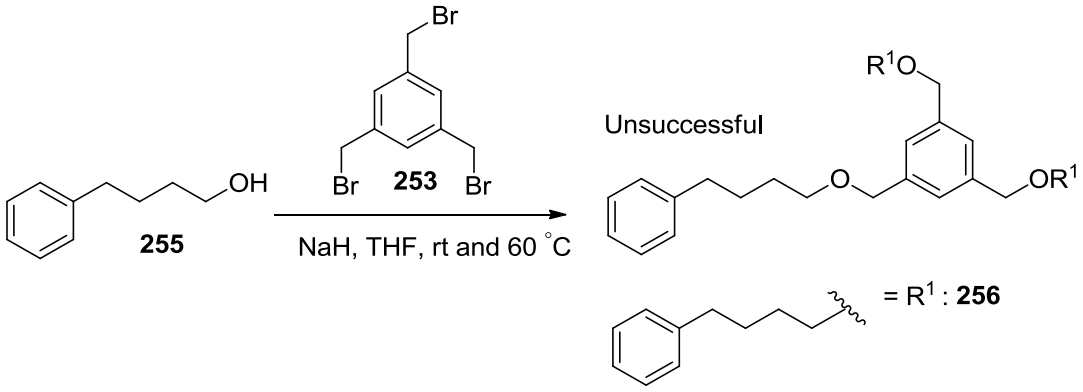
2.3.4 Ether-linked *N*-alkylated ligands.

The synthesis of ether-linked *N*-alkylated ligand was unsuccessful using NaH in THF with **236** and 1,3,5-tris(bromomethyl)benzene **253** at rt (Scheme 96).[29e] In the attempt to not waste ligand **236**, 4-phenyl-1-butanol **255** was first used in order to optimize conditions for coupling with **253**.



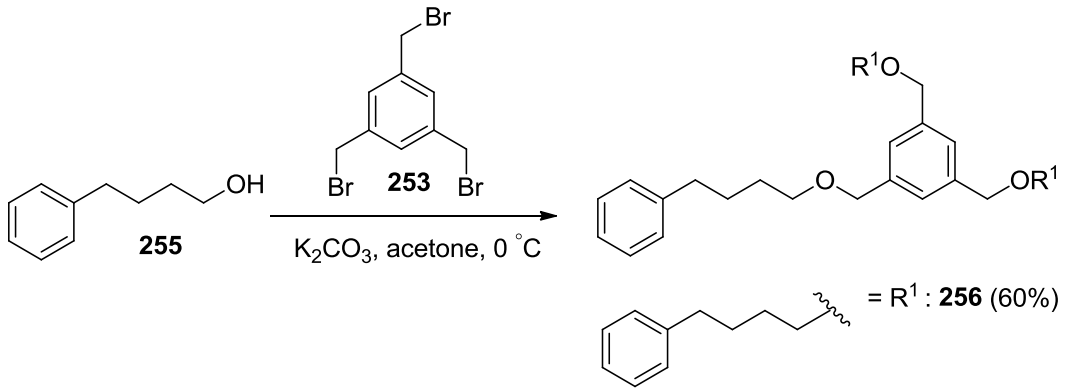
Scheme 96. Attempted synthesis of a "trimeric" ether-linked ligand **254** using **236** and **253** failed.

Using NaH in THF, the coupling was repeated as previously shown, but using 4-phenyl-1-butanol **255** with 1,3,5-tris(bromomethyl)benzene **253**. The reaction was carried out at rt and at 60 °C, but the coupling was unsuccessful on both occasions (Scheme 97).



Scheme 97. Attempted synthesis of a "trimeric" ether-linked test ligand **256** using **255** and **253** failed.

However when the coupling of **255** with **253** was carried out using K_2CO_3 in acetone at 0 °C,[29f] the coupling was successful (Scheme 98, Figure 35). However due to lack of time further studies were not conducted in this area.



Scheme 98. Synthesis of a "trimeric" ether-linked test ligand **256** using **255** and **253**.

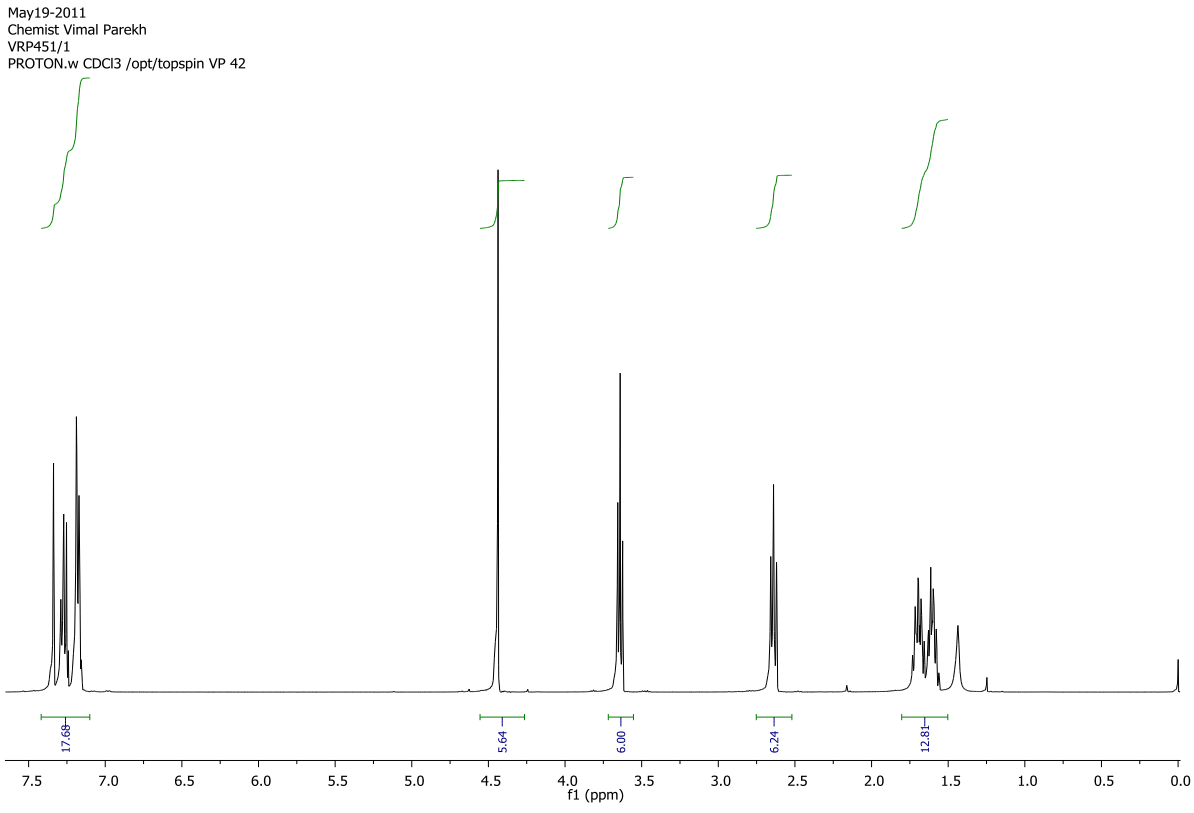
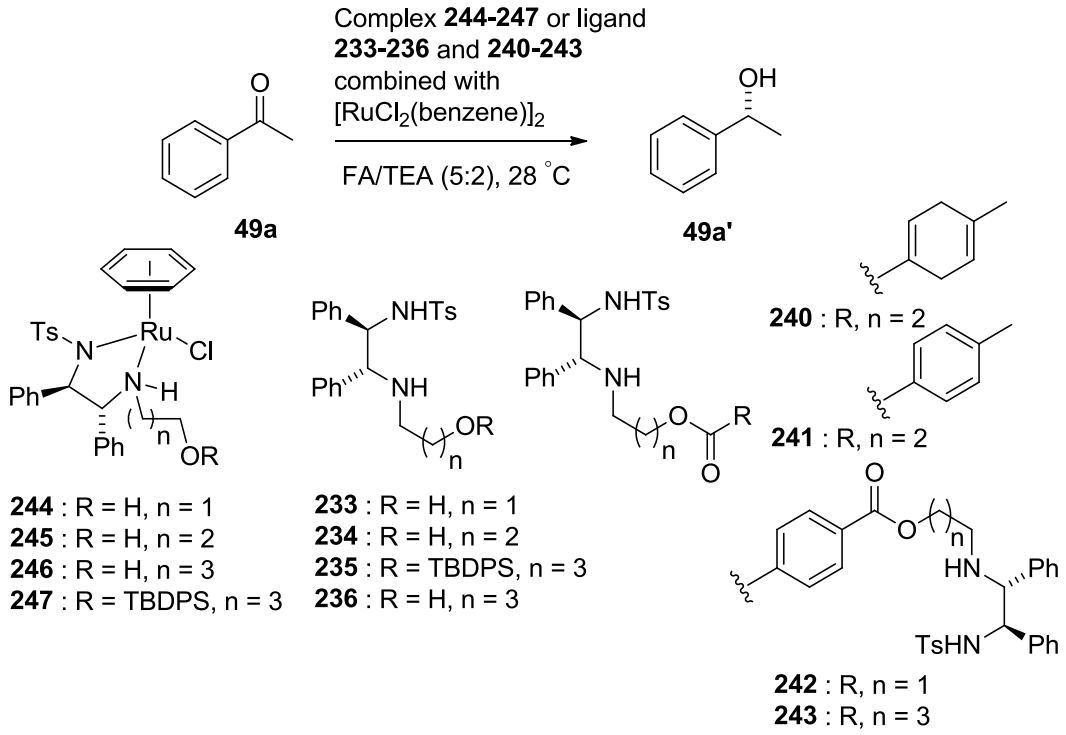


Figure 35. ^{1}H NMR of "trimeric" ether-linked test ligand **256**.

2.3.5 Aymmetric transfer hydrogenation reduction using Ru(II) *N*-alkylated complexes and ligands.

In the ATH of acetophenone, each of the catalysts, both pre-prepared, and formed *in situ*, proved to be effective and gave a product of high enantiomeric excess (Table 51). The *N*-alkylated complexes were somewhat less active than the unsubstituted and "tethered" complexes, however, with a typical reaction time of 4 days being required for full reduction at rt at 0.5 mol% catalyst loading. Catalyst **244**, with the shortest chain, was the least active, requiring 10 days to achieve >99% conversion to product. This may indicate that there is some reversible interaction of the OH group with the Ru(II) atom, thereby reducing its effective concentration in the reaction. This would have a close analogy to the effect observed by White for hydroxyethyl-substituted complex **227**.[28g] As the chain becomes longer, this reduction in activity is attenuated and, for the 4C complex, there is essentially no difference in activity between the silylated **247** and the free OH complex **246**, as would be expected on entropic grounds. In general, the isolated complexes were more active than the complexes formed *in situ* (Scheme 99, Table 51).



Scheme 99. ATH reduction of acetophenone **49a**, using complex **244-247** and ligands **233-236** and **240-243** in conjunction with $[RuCl_2(benzene)]_2$ (S/C = 200).

Entry	Catalyst	Time (days)	Conv. (%)	ee (%)/ Config. (*R*/*S*)
1	**233/Ru**	13	>99	92 *R*
2	**234/Ru**	8	31	92 *R*
3	**235/Ru**	6	>99	95 *R*
4	**236/Ru**	6	93	94 *R*
5	**244**	3	88	93 *R*
6	**245**	2	>99	94 *R*
7	**246**	2	>99	95 *R*
8	**247**	2	>99	95 *R*
9	**240/Ru**	5	98	95 *R*
10	**241/Ru**	5	97	96 *R*
11	**242/Ru**	5	92	96 *R*
12	**243/Ru**	8	>99	95 *R*

Table 51. ATH reduction of acetophenone **49a**, using complex **244-247** and ligands **233-236** and **240-243** in conjunction with $[RuCl_2(benzene)]_2$ (S/C = 200).

The ester-terminated complexes formed **240-243** were also efficient catalyst for the ATH of acetophenone, giving products of 95-96% ee in high conversion. The presence

of a nearby ester appears entirely compatible with catalyst activity. It should be noted that all of the reactions in Table 51 were followed over time order to confirm that no racemisation was taking place during their course (Table 52-63).

In conclusion, complexes containing a straight-chain substituent attached to a hydroxyl, ether or ester function also act as effective catalysts. This may represent a useful means for the attachment of the catalyst to a heterogeneous support.

Conversions and enantioselectivities of complexes 244-247 and ligands 233-236 and 240-243 over time.

Catalyst **244**

Time	Conversion	Enantiomeric excess (%)
1 hr	1.3	-
5 hrs 40 mins	6.4	92
24 hrs 10 mins	28	92
48 hrs 40 mins	63	93
72 hrs 40 mins	88	93

Table 52.

Catalyst **245**

Time	Conversion	Enantiomeric excess (%)
16 hrs 40 mins	87	94
25 hrs 10 mins	96	95
42 hrs 10 mins	>99	94

Table 53.

Catalyst **246**

Time	Conversion	Enantiomeric excess (%)
16 hrs 40 mins	93	95
25 hrs 10 mins	98	95
42 hrs 10 mins	>99	95

Table 54.

Catalyst **247**

Time	Conversion	Enantiomeric excess (%)
16 hrs 40 mins	94	95
25 hrs 10 mins	98	96
42 hrs 10 mins	>99	95

Table 55.

Ligand **233**

Time	Conversion	Enantiomeric excess (%)
2 hrs 50 mins	-	-
23 hrs 5 mins	7.8	91
94 hrs 20 mins	60	90.4
141 hrs 50 mins	89	91
311 hrs 50 mins	>99	92

Table 56.

Ligand **234**

Time	Conversion	Enantiomeric excess (%)
17 hrs 45 mins	10	93
41 hrs 45 mins	20.5	93
116 hrs 45 mins	30	92
138 hrs 45 mins	30	92
185 hrs 45 mins	31	92

Table 57.

Ligand **235**

Time	Conversion	Enantiomeric excess (%)
17 hrs 45 mins	24	94
41 hrs 45 mins	73.4	95
116 hrs 45 mins	>99	95
138 hrs 45 mins	>99	95

Table 58.

Ligand **236**

Time	Conversion	Enantiomeric excess (%)
17 hrs 45 mins	25	93
41 hrs 45 mins	67.3	94
116 hrs 45 mins	93	94
138 hrs 45 mins	93	94
185 hrs 45 mins	93	93.4

Table 59.

Ligand **240**

Time	Conversion	Enantiomeric excess (%)
16 hrs	51	96
41 hrs	88	97
113 hrs	98	95

Table 60.

Ligand **241**

Time	Conversion	Enantiomeric excess (%)
16 hrs	46	96
41 hrs	86	95
113 hrs	97	96

Table 61.

Ligand **242**

Time	Conversion	Enantiomeric excess (%)
4 hrs	4	89
23 hrs	48	95
46 hrs 30 mins	78	97
119 hrs 30 mins	92	96

Table 62.

Ligand **243**

Time	Conversion	Enantiomeric excess (%)
17 hrs 45 mins	11	94

41 hrs 45 mins	40.1	95
116 hrs 45 mins	93	95
138 hrs 45 mins	96	95
185 hrs 45 mins	>99	95

Table 63.

2.4 Further work on the synthesis of "tethered" Ru(II) catalysts.

Further work that was carried out during the course of this PhD project, included the attempted synthesis of catalysts **257-261** (Figure 36).

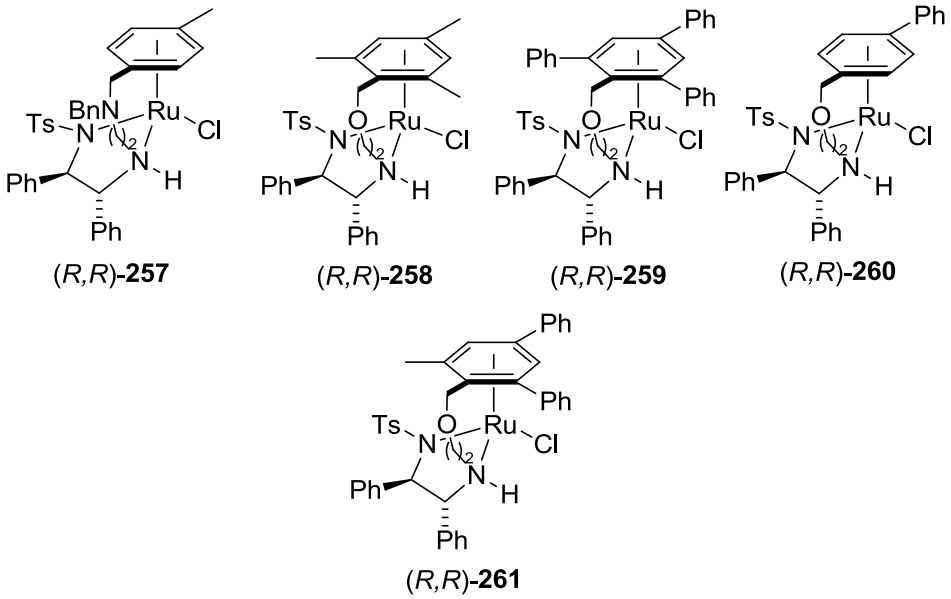
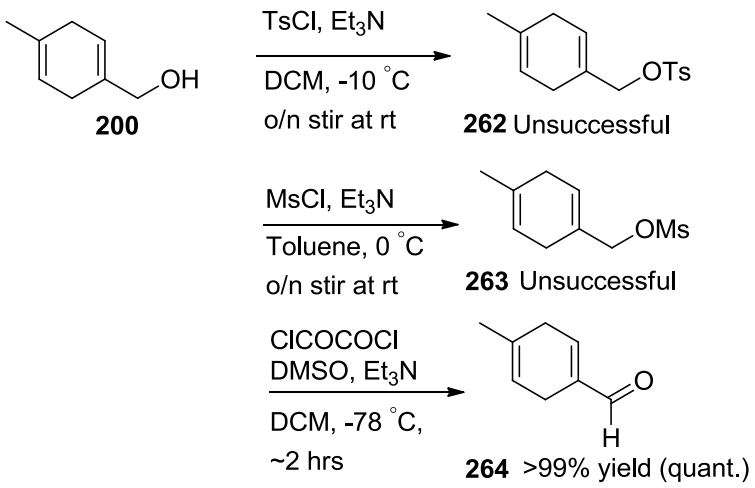


Figure 36. Attempted synthesis of the Ru(II) "tethered" catalysts **257-261**.

2.4.1 Synthesis of the *N*-linked "tethered" catalyst 257.

The synthesis of the *N*-linked "tethered" catalyst was the next task in this project after the successful synthesis of the ether-linked catalyst **207**, as bulkier groups can be functionalized on the "tether", and its effects on ATH reductions is worth investigating (Section 1.4.7). In order to proceed with the synthesis, it was vital that **200** was converted into a good leaving group for the successful insertion of benzylamine. The attempts to tosylate and mesylate proved to be unsuccessful as the products formed **262/263**[20a] were very sensitive and possibly reacted with other sources/impurities

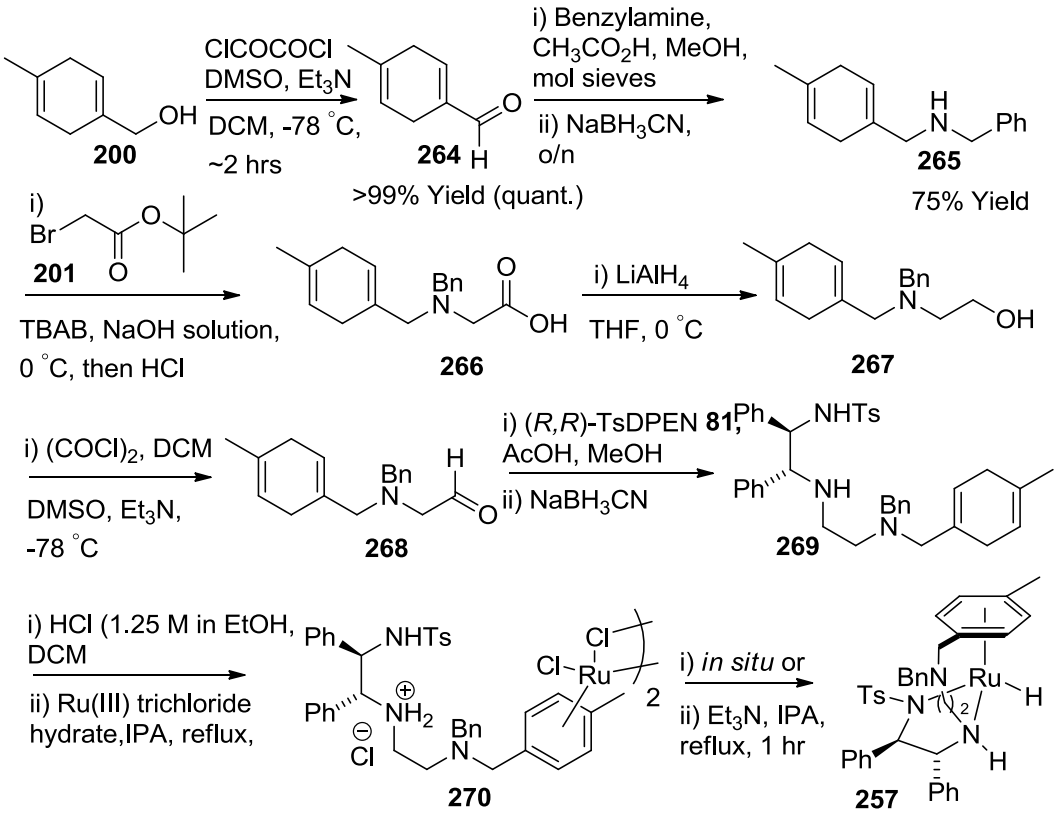
present in solution. To overcome this problem, **200** was successfully converted in to an aldehyde so that reductive amination with benzylamine could be carried out. 4-methylcyclohexa-1,4-dienecarbaldehyde **264** via swern oxidation[20a] with the use of oxalylchloride, dimethylsulfoxide and triethylamine in dichloromethane at -78 °C was successfully formed in >99% yield (quant.) (Scheme 100).



Scheme 100. Attempted conversion of the alcohol **200** in to a good leaving group.

Reductive amination was carried out in methanol using **264**, benzylamine and glacial acetic acid to form an imine, which then was reduced to give *N*-Benzyl (4-methylcyclohexa-1,4-dienyl) methanamine[20a] **265** as a yellow oil in 75% yield using sodium cyanoborohydride. The steps that need to be carried out for the completion of this catalyst will now be outlined. The amine **265** needs to be coupled with *tert*-butylbromoacetate **201** in NaOH solution and using TBAB to give **266**,[27b] which would then be reduced with $LiAlH_4$ in THF to give **267**[17j], and oxidised via Swern oxidation to form **268**[20a]. Reductive amination in methanol would then be carried out using **268**, *R*,*R*-TsDPEN **81** and glacial acetic acid to form an imine, then reduced to give **269**[20a] using sodium cyanoborohydride. The final step would then be the complexation of **269**.HCl salt which is formed by the addition of hydrochloric acid in DCM, and then

complexation with ruthenium(III) trichloride hydrate in IPA at reflux temperature, to form **270**[20a], which *in situ* would form **257** or can isolate the monomer **257** by the reaction of dimer **270** with Et_3N in IPA for 1 hr[20a] (Scheme 101). Due to insufficient time, the synthesis could not be completed.



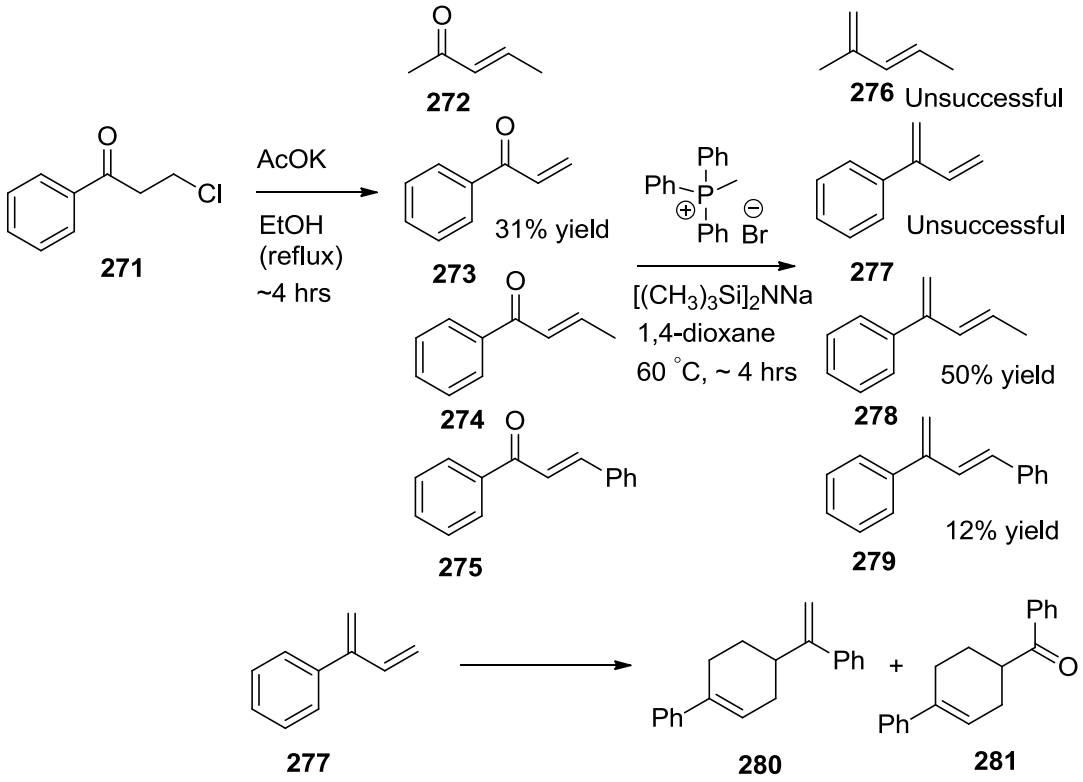
Scheme 101. Proposed synthesis of the *N*-linked "tethered" catalyst **257**. This synthesis was not completed.

2.4.2 Synthesis of the ether-linked "tethered" Ru(II) catalyst with functionalized arene ring.

Investigations into the modification of the η^6-arene ring have been carried out previously in the Wills group, preparing derivatives of "tethered" catalysts **148-151** and **152-155** with a variety of functional groups on the arene ring using a [4 + 2] cycloaddition step. This area was further investigated, with the replacement of the alkyl "tether" with the ether-linked "tether" and having monotosyl diamine ligand replacing

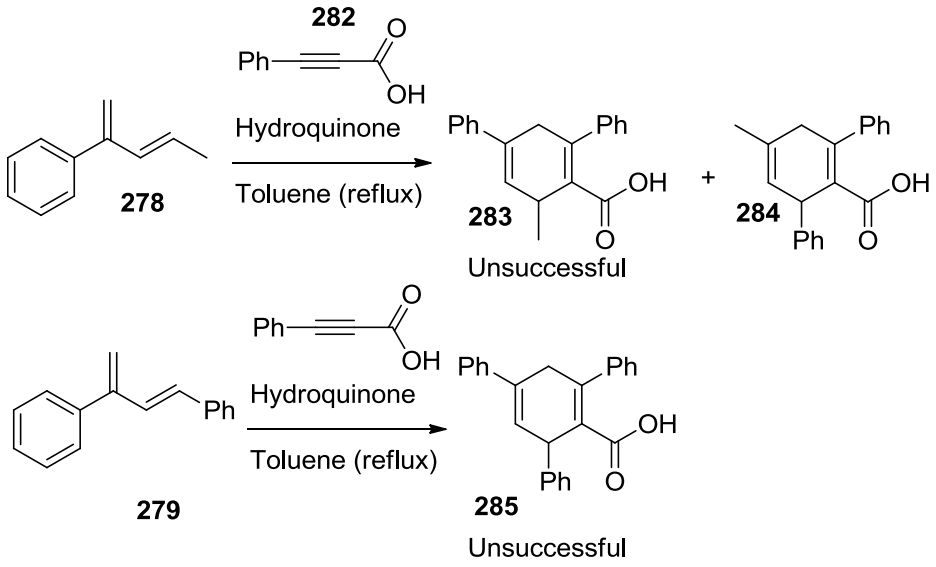
the previously used amino alcohol and sulfonylated diamine. It was previously demonstrated by Noyori that mesitylene or *p*-cymene arene ligands were less reactive than unsubtituted benzene, but gave better enantioselectivities. For this reason, the mesitylene functionality was incorporated in to the original ether-linked "tethered" catalyst **206** (forming **207** *in situ*) to give **258**. The synthesis of catalysts **259-261** were carried out as they seemed interesting, and because useful information could be generated with the use of these catalysts for the ATH reduction of aromatic and dialkyl ketones.

The attempted synthesis of the isoprenes required for the cycloaddition step has been shown in Scheme 102. Substrate **272** and **274-275** were readily available; however **273** had to be prepared by the reaction of **271** with AcOK in refluxing ethanol, giving **273** in 31% yield.[30a] The conversion of the C=O group to C=C was unsuccessful with **272** using methyltriphenylphosphonium bromide, sodium hexamethyldisilazide in 1,4 dioxane at 60 °C,[30b] as it was very volatile and difficult to isolate. The same reaction using **273** had formed a mixture of **280** and **281** instead of **277**. It was however successful for the formation **278** and **279** (Scheme 102).



Scheme 102. Synthesis of the required isoprene **276**-**279**, with successful product formation of **278**-**279**, but unsuccessful for **276**-**277**.

Cycloaddition reaction of **278** and **279** using **282** and hydroquinone in refluxing toluene had failed to deliver the expected products, instead giving decomposed material (Scheme 103).

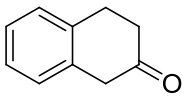


Scheme 103. Attempted cycloaddition reaction of **278** and **279** with **282**. These reactions were unsuccessful.

3. Appendix; Additional studies completed within the project.

3.1 Asymmetric transfer hydrogenation reductions of imines derived from β-tetralone 223.

An early objective in this project was to synthesize a series of useful acyclic imine substrates derived from β-tetralone **223** (Figure 37), and then examine their asymmetric reduction using Ru(II) untethered and "tethered" complexes. Synthesizing acyclic imines derived from **223** is unusual, rare and it produces some interesting amine targets as shown in Scheme 104 and Scheme 105.

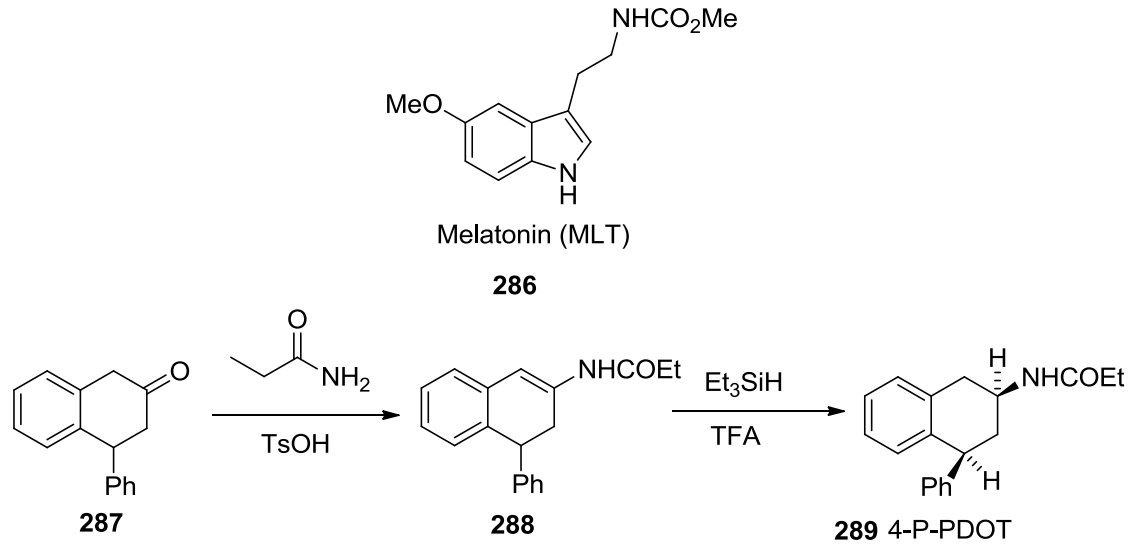


223

Figure 37. Structure of β-tetralone **223**.

In mammals, melatonin (*N*-acetyl-5-methoxytryptamine, MLT) **286**, a neurohormone modulates a variety of cellular, neuroendocrine and physiological processes through the activation of atleast two high-affinity G-protein coupled receptors, named MT_1 and MT_2.[31a] Piersanti[31b] developed a novel, efficient and diastereoselective procedure for the gram-scale synthesis of *cis*-4-phenyl-2-propionamidotetralin (4-P-PDOT) **289**, a selective MT_2 melatonin receptor antagonist. The synthetic strategy involved the conversion of 4-phenyl-2-tetralone **287** derived from **223** to enamide **288** by refluxing under nitrogen, **287** with propionamide and p-toluenesulfonic acid in toluene using Dean-Stark apparatus affording **288** as a light yellow oil in 95% yield after column

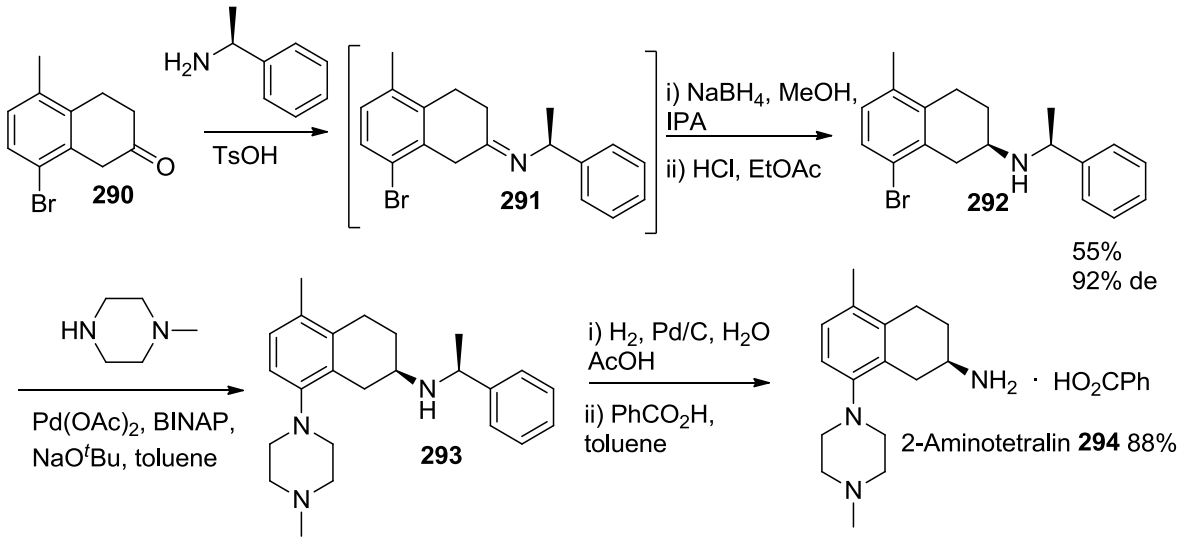
chromatography and recrystallisation. A diastereoselective reduction of **288** was carried out by cooling down a solution of **288** in trifluoroacetic acid to -10 °C followed by the dropwise addition of triethylsilane affording **289** in 71% yield after column chromatography and recrystallisation[31c] (Scheme 104).



Scheme 104. Synthesis of 4-P-PDOT **289**, a selective MT_2 melatonin receptor antagonist.

The pharmacological importance of the 2-aminotetralin (2-amino-1,2,3,4-tetrahydronaphthalene) **294** structure has been known for a long time. Initially, aminotetralins were characterized by their sympathomimetic action (causing mydriasis, contraction of the uterus, changes in blood pressure and respiration, and increased intestinal motility in test animals). During the late sixties the dopaminergic activity of 2-aminotetralins was identified which led to an active synthesis program. For the synthesis of a complex **294** carried out by Hans-Jurgen Federsel (Astrazeneca), the nitrogen at the stereogenic centre was introduced by a reductive amination of 8-bromo-5-methyl-3,4-dihydronaphthalen-2(1*H*)-one **290** derived from **223** with phenylethylamine, firstly forming the intermediate imine **291** with the addition of p-toluenesulfonic acid, and then forming the resulting amine **292** with a sodium

borohydride reduction. The Buchwald-Hartwig approach with palladium acetate in the presence of BINAP afforded the piperazine coupled product **293**. Finally carrying out a hydrogenation followed by the addition of benzoic acid resulted in the formation of the complex **294** in 88% yield[31d] (Scheme 105).



Scheme 105. Synthesis of a complex 2-Aminotetralin **294**, with 'pharmaceutical significance'

A series of β-tetralone derived imines that were considered worthy of investigation are shown in Figure 38.

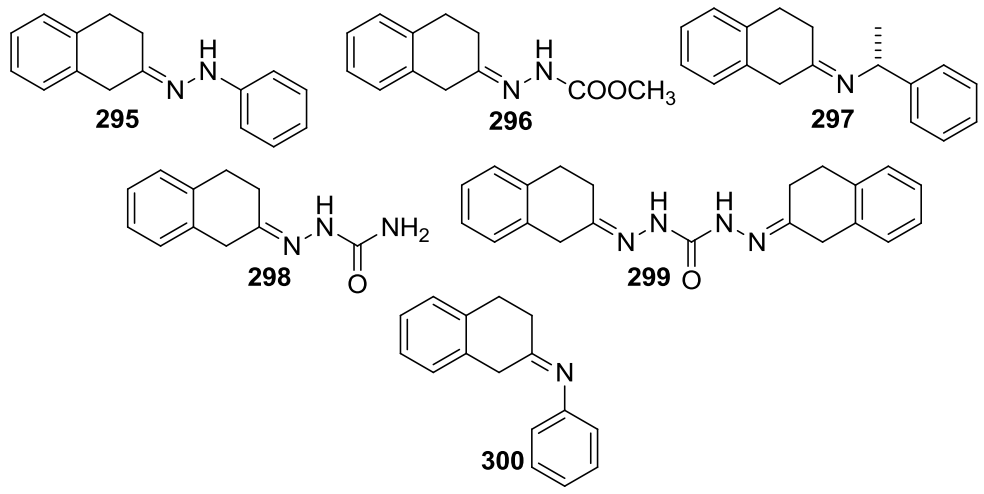
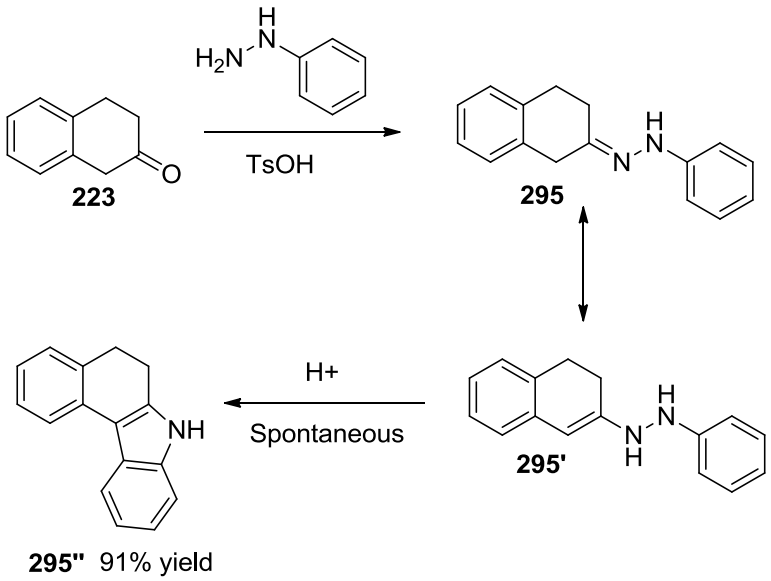


Figure 38. C=N reduction substrates

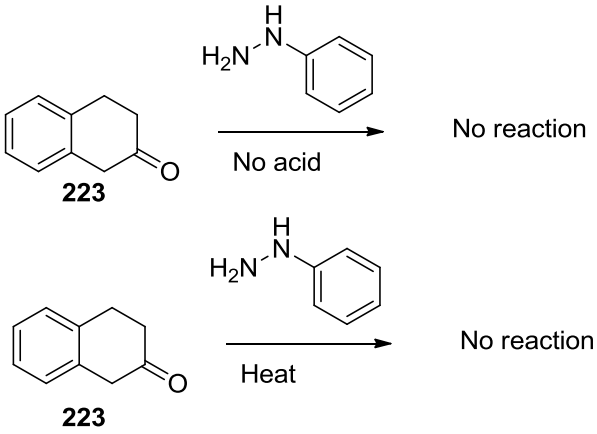
Attempted synthesis of (*E*)-1-(3,4-dihydronaphthalen-2(1*H*)-ylidene)-2-phenylhydrazine 295.

The first objective was to synthesize **295**, however the reaction of a phenylhydrazine with **223** initially forms **295**, but this can then isomerize to the respective enamine **295'** (or 'ene-hydrazine'). After protonation, a cyclic [3,3]-sigmatropic rearrangement can occur producing an imine. The resulting imine can form a cyclic aminoacetal (or aminal), which under acid catalysis eliminates NH_3, resulting in the energetically favorable aromatic indole **295''** (Scheme 106). This is the Fischer indole synthesis. Care must be taken to stop at the imine stage.



Scheme 106. Reaction of **223** with phenylhydrazine to give **295''** instead of **295**.

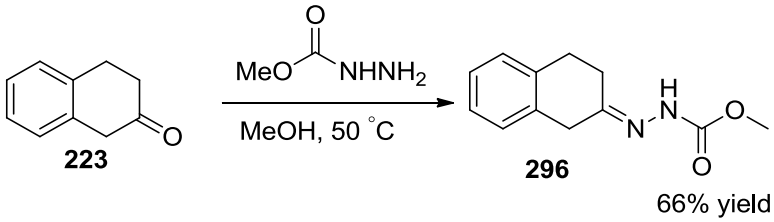
In the event, the condensation reaction under acidic conditions resulted in the formation of the aromatic indole **295''** (in 91% Yield as an orange-red oil) and not the desired **295**. This particular reaction proved to be unsuccessful without acidic conditions and using heat in an attempt to avoid the Fischer indole reaction (Scheme 107).



Scheme 107. Reaction of **223** with phenylhydrazine, with heat and without acidic conditions.

Synthesis of Methyl [3,4-dihydro-2(1*H*)-naphthalen-ylidene]-hydrazinecarboxylate 296.

The next objective was to successfully synthesize **296** using a method in the literature published by Beam**.**[31e] The reaction was carried out by the addition of methylhydrazinocarboxylate and **223** in methanol, stirring at 50 °C overnight affording **296** as orange-white crystals in 66% yield[31f] (Scheme 108). As there were distinctive impurities present in the crude product as shown by NMR analysis, purifying the crude product was necessary before any reductions were carried out.



Scheme 108. Reaction of **223** with methylhydrazinocarboxylate to give **296**.

Purification methods such as Column chromatography, Kugelrohr distillation and recrystallization all proved unsuccessful.

The structural properties of **296** were worthy of further investigation, therefore a variable temperature NMR of **296** was recorded at 25 °C, 40 °C and 50 °C (Figure 39).

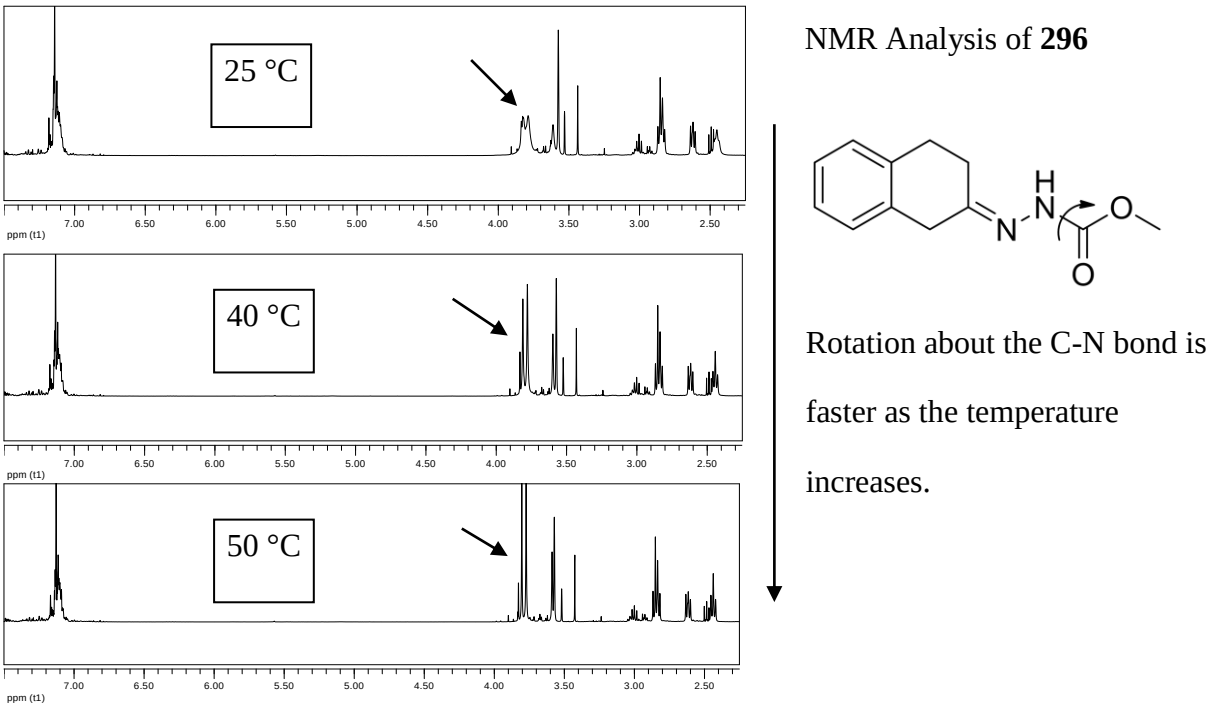


Figure 39. NMR analysis of **296** at various temperatures.

The results were informative, as the peaks marked with an arrow are increasing in height as the temperature is increased. This indicates that the speed of rotation about the C-N bond is increasing with increasing temperature, as the NMR machine is unable to differentiate between the two different isomers causing a compressed tall peak to appear. The large energy barrier between *E*/*Z* isomers clearly eliminates the possibility of 'flipping' of the *E* form to the *Z* form (rotation about the N-N bond) and vice versa. Rotation about the C-N bond is of low energy barrier, and can be held responsible for the change in NMR with increasing temperature (Figure 39-40).

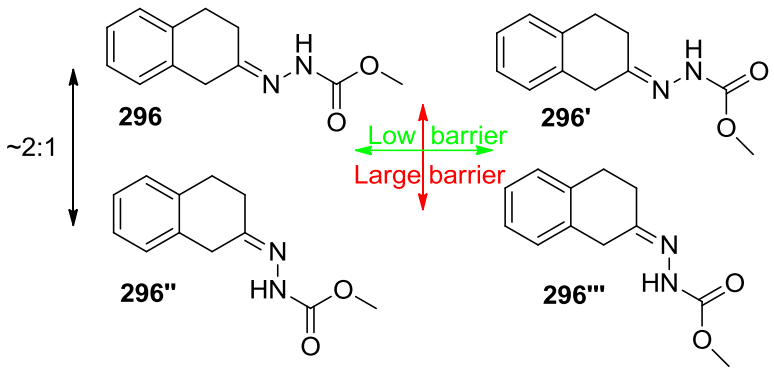
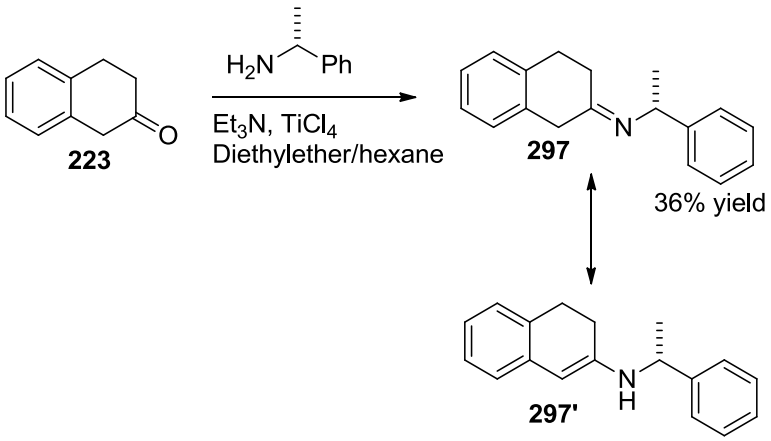


Figure 40. The four different isomers of **296.**

This substrate was proving to be quite problematic and so it was not further used as part of this project.

Synthesis of (*R*,*E*)-*N*-(3,4-dihydronaphthalen-2(1*H*)ylidene)-1-phenylethanamine 297.

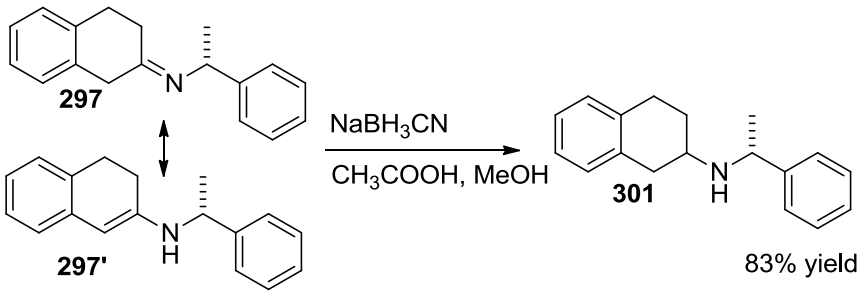
The synthesis of **297** was carried out using (*R*)-α-methylbenzylamine and **223,** which was difficult at first as various procedures from previous literature were tested out, all proving to be unsuccessful. But the procedure published by Carlson, Larsson and Hansson[31g] in 1992 proved to be successful giving **297** which is in equilibrium with enamine **297'**, using titanium tetrachloride as the water trapping agent, deoxygenating every reagent/solvent used, and keeping the reaction under argon at all times, even while filtering out the precipitate formed. The dark green crude product formed was purified using Khugelrohr distillation, giving a clear yellow oil in 36% yield (Scheme 109). This particular product is highly air sensitive, light sensitive and has to be stored at low temperatures in order to avoid colour change and decomposition.



Scheme 109. Reaction of **223** with (*R*)-alpha-methylbenzylamine giving **297**.

Reductions using sodium cyanoborohydride and the untethered catalyst **38** were carried out on **297** to try and obtain *N*-((*R*)-1-phenylethyl)-1,2.3,4-tetrahydronaphthalen-2-amine **301**.

Sodium cyanoborohydride reduction was successfully carried out to give a standard sample of both diastereoisomers of **301** in 83% yield, as confirmed by ^{1}H NMR and MS analysis (Scheme 110, Figure 41).



Scheme 110. Reduction of **297** using $NaBH_3CN$, giving the amine **301**.

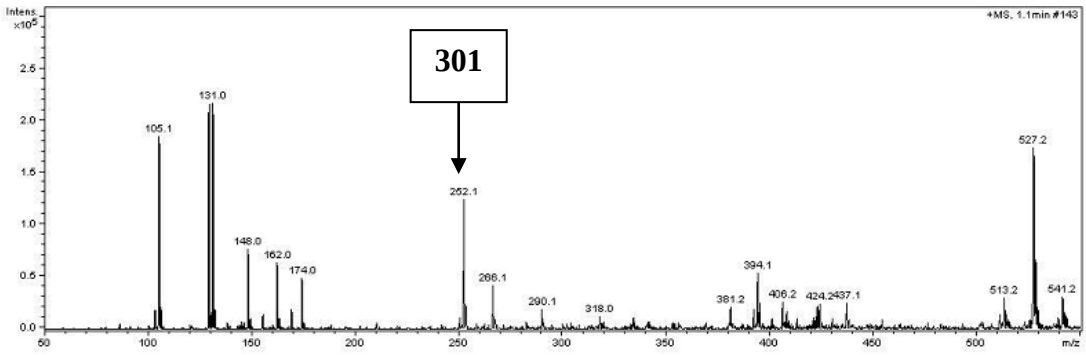
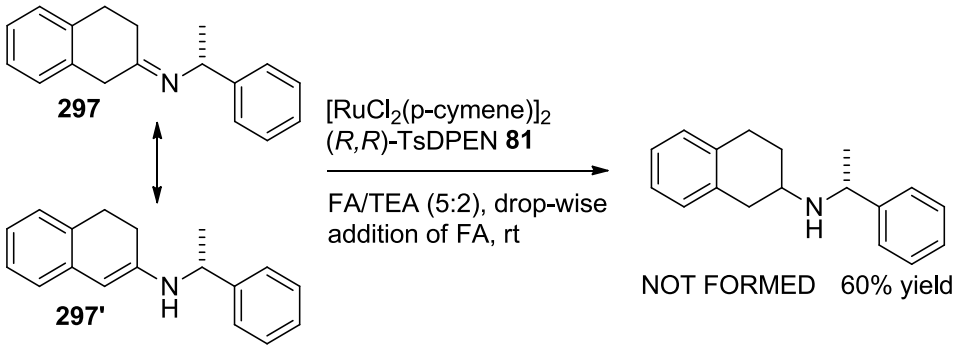


Figure 41. LR MS of amine **301**.

Reduction using the untethered catalyst **38** was unsuccessful as shown by LR MS (Figure 42) and ^{1}H NMR analysis (Scheme 111), giving a ~50 : 50 mixture of β-tetralone **223** and an unknown product, which couldn't be identified. The result was also quite similar when a few attempted reductions were carried out using "tethered" catalyst **163b** instead of the untethered catalyst **38**.



Scheme 111. Reduction of **297** using the untethered catalyst **38** (S/C = 200).

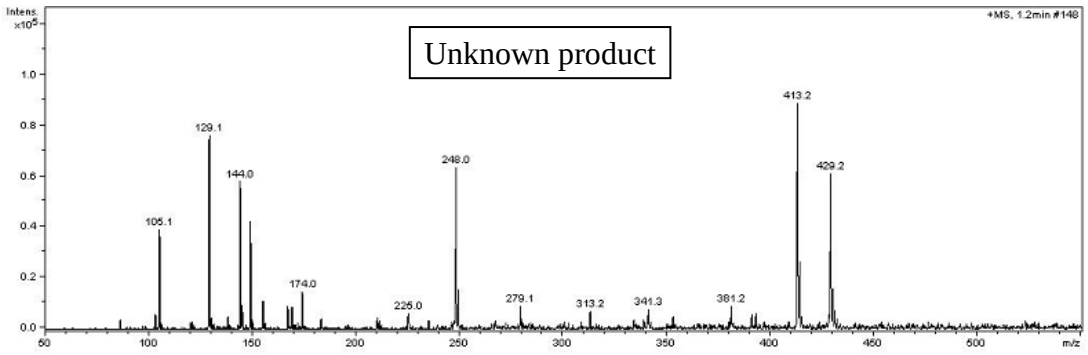
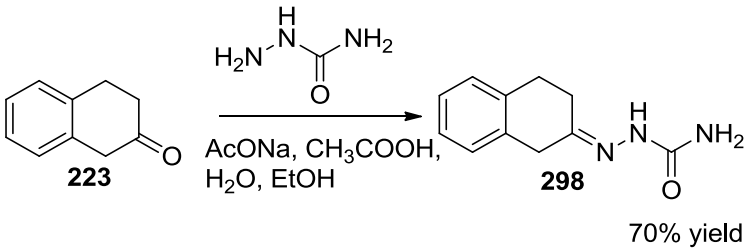


Figure 42. LR MS of the unknown product formed from the reduction of **297** with the untethered catalyst **38**.

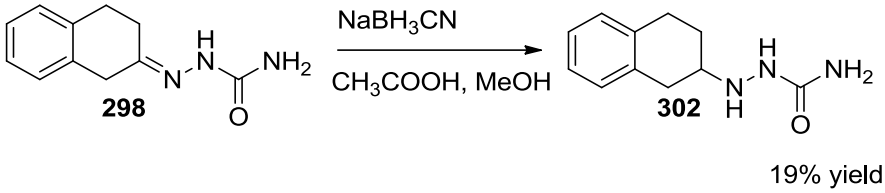
Synthesis of (*E*)-1-(3,4-dihydronaphthalen-2(1*H*)-ylidene)semicarbazide 298.

The preparation of **298** was quite straight forward and followed a literature precedent published by Dimmock and Pandeya.[31h] Reacting a mixture of semicarbazide hydrochloride, sodium acetate and water with a solution of **223** in ethanol gave **298** as white crystals in 70% yield (Scheme 112). The reductions carried out with **298** were unsuccessful as a lot of solvent was required to dissolve **298**. The two recommended solvents for ATH reductions giving best yields and conversion rates are acetonitrile and methanol, however neither was able to dissolve the product using recommended quantities.



Scheme 112. Reaction of **223** with semicarcarbazide, giving **298**.

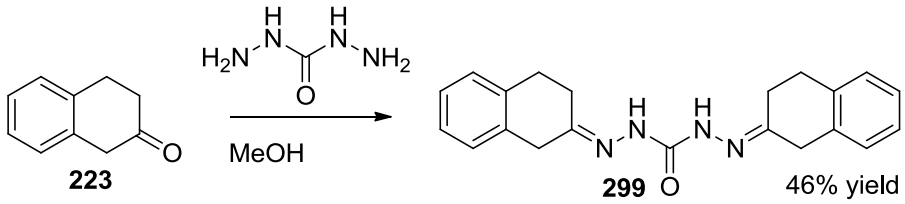
The racemic standard of **298** was however successfully prepared using $NaBH_3CN$, acetic acid in methanol, giving **302** after column chromatography (Scheme 113).



Scheme 113. Reduction of **298** using $NaBH_3CN$ giving **302**.

Synthesis of (1*E*,5*E*)-1,5-bis(3,4-dihydronaphthalen-2(1*H*)-ylidene)carbonohydrazide 299.

Synthesis of **299** was successfully carried out using the same literature published by Dimmock and Pandeya[31h] for synthesis of **298**. The addition of carbohydrazide in methanol to **223** in methanol, and after the solution was stirred for 20 mins, **299** had formed as grey crystals in 46% yield (Scheme 114). The crude product contained some impurities, which even after recrystallisation had remained.

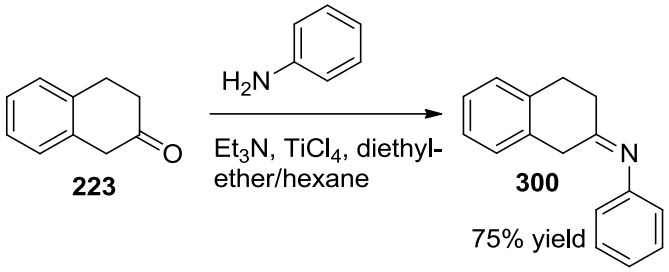


Scheme 114. Reaction of **223** with carbohydrazide, giving **299**.

Product **299** encountered similar solubility issues that were previously observed for **298**.

Synthesis of (*Z*)-*N*-(3,4-dihydronaphthalen-2(1*H*)-ylidene)benzenamine 300.

The final objective was to successfully synthesize **300.** The synthesis of **300** was carried out by following the same procedure as for making **297** as this substrate has not been synthesised before.[31g] An orange-red oil was formed in 75% yield (Scheme 115). ^1H NMR and LR MS analysis of the crude product showed the presence of **300**. Distillation and various purification methods such as column chromatograph had proved to be unsuccessful, giving decomposed material.



Scheme 115. Reaction of **223** with aniline, giving **300**.

Due to a series of implications in this project, work in this area was not further carried out.

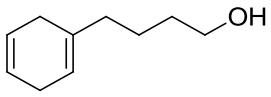
4. General Experimental.

All the air sensitive reactions were carried out under an argon or nitrogen atmosphere. Room temperature (rt) refers to ambient temperature (20-22 °C), 0 °C refers to an ice slush bath and -78 °C refers to a dry ice acetone bath. Heated experiments were conducted using thermostatically controlled oil baths or Asynt aluminium heating blocks. Reactions were monitored by Thin Layer Chromatography (TLC) using aluminium backed silica gel 60 (F_{254}) plates, visualised using $UV_{254\ nm,}$ PMA, iodine, potassium permanganate and ninhydrin dips as appropriate. ^{13}C-NMR spectra were recorded on a Bruker DPX-300 (300 MHz) or a Bruker DPX-400 (400 MHz). All chemical shifts are reported in ppm downfield from TMS (Me_4Si). Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H-NMR is reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), octet (oct), double doublet (dd), triple triplet (tt), broad singlet (br s), broad multiplet (br m) and multiplet (m). Mass spectra were recorded on an Esquire 2000. High resolution mass spectra were recorded on Bruker Micro ToF. Infrared spectra were recorded on PerkinElmer spectrum100. The optical rotations were measured on Optical Activity Ltd. AA-1000 Polarimeter. The Chiral HPLC measurements were carried out on HPLC consisting of a Gilson 811B Dynamic Mixer, a Gilson 805 Monometer Module, a Gilson 305 Piston Pump, Merck-Hitachi L-4000 UV detector linked to HEWLETT PACKARD 3396 Series II integrator with CHIRAL PAK IA/IB column (0.46 cm x 25 cm) or CHIRAL CEL OD-H/OD column (0.46 cm x 25 cm). The chiral GC measurements were done on HEWLETT PACKARD 5890 linked to HEWLETT PACKARD HP3396A integrator or PERKIN-ELMER 8500 chromatography linked to PC running DataApex Clarity software with Chrompak CP-Chirasil Dex Cβ column. Melting points were determined on a Stuart scientific melting point apparatus and are uncorrected. Purification of compounds was carried out by

using flash column chromatography using silica gel of mesh size 230-400/ Florisil of mesh 100-200 or Kugelrohr distillation using BÜCHI GKR-51.

4.1 Procedures from Section 2.1

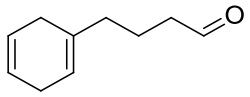
Synthesis of 4-(cyclohexa-1,4-dienyl)butan-1-ol (303).



This is a known compound and has been fully characterised.[20a]

A solution of 4-phenylbutan-1-ol (3.30 g, 3.39 cm^3, 22 mmol) in ethanol (10 cm^3) was slowly added to a refluxing solution of ammonia (250 cm^3) containing ethanol (70 cm^3) at -78 °C while stirring. Small cleaned (with hexane) sodium pieces were added to the reaction mixture until the blue colour persisted. After the addition of sodium over the course of 7 hours with regular additions of ethanol (5-10 cm^3) to facilitate stirring, the reaction mixture was then left overnight to allow the remaining ammonia to evaporate. Saturated $NH_4Cl_{(aq)}$ (100 cm^3) was added to the reaction, which was then extracted using DCM (3 x 30 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **303** as a light orange oil (3.30 g, 21.68 mmol, >99%); δ_H (400 MHz, $CDCl_3$) 5.75-5.67 (2 H, m, *H*C=C*H*), 5.48-5.40 (1 H, m, C=C*H*), 3.65 (2 H, t, *J* 6.3, CH_2OH), 2.70-2.67 (2 H, m, C=CCH_2C=C), 2.60-2.55 (2 H, m, C=CCH_2C=C), 2.00 (2 H, t, *J* 7.0, CH_2CH_2CH_2CH_2OH), 1.65-1.45 (4 H, m, CH_2CH_2CH_2CH_2OH) and 1.31 (1 H, br s, O*H*); δ_C (101 MHz, $CDCl_3$) 134.74 (*C*), 124.31 (*C*H), 124.27 (*C*H), 118.45 (*C*H), 62.63 (*C*H_2), 37.16 (*C*H_2), 32.33 (*C*H_2), 28.86 (*C*H_2), 26.73 (*C*H_2) and 23.43 (*C*H_2). The data matched that previously reported.

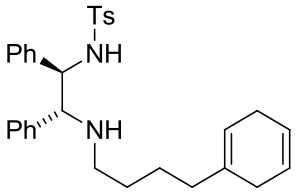
Synthesis of 4-(cyclohexa-1,4-dienyl)butanal (304).



This is a known compound and has been fully characterised.[20a]

The solution of oxalylchloride (2 M in DCM, 7.78 cm^3, 15.55 mmol) in anhydrous DCM (20 cm^3) was cooled to -78 °C, and to this was slowly added DMSO (2.21 cm^3, 31.10 mmol) in DCM (10 cm^3) by syringe. The solution was stirred for 30 minutes at -78 °C before 4-(cyclohexa-1,4-dienyl)butan-1-ol **303** (1.82 g, 11.96 mmol) in DCM (30 cm^3) was slowly added at the same temperature. After stirring for 45 minutes at -78 °C, Et_3N (10 cm^3, 71.69 mmol) was added, and the reaction mixture was allowed to warm up to rt. After 60 minutes, water (75 cm^3) was added, and the mixture was extracted with DCM (3 x 40 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **304** as a light orange oil (1.82 g, 12.12 mmol, >99% quantitative conversion, includes traces of solvent); δ_H (400 MHz, $CDCl_3$) 9.77 (1 H, s, C*H*=O), 5.74-5.66 (2 H, m, *H*C=C*H*), 5.42 (1 H, br s, C=C*H*), 2.72-2.63 (2 H, m, C=CCH_2C=C), 2.62-2.55 (2 H, m, C=CCH_2C=C), 2.42 (2 H, t, *J* 7.3, $CH_2CH_2CH_2$CHO), 1.99 (2 H, t, *J* 7.3, $CH_2CH_2CH_2$CHO) and 1.75 (2 H, quin, *J* 7.3, $CH_2CH_2CH_2$CHO); δ_C (101 MHz, $CDCl_3$) 202.63 (*C*H=O), 133.78 (*C*), 124.32 (*C*H), 124.23 (*C*H), 119.46 (*C*H), 43.26 (CH_2), 37.16 (CH_2), 28.86 (CH_2), 26.71 (CH_2) and 20.00 (CH_2). The data matched that previously reported for this compound.

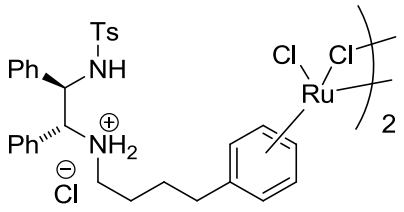
Synthesis of (*R*, *R*)-*N*-(4-cyclohexa-1,4-dienyl)butyl)-1,2-diphenyl-*N'*-tosylethane-diamine (162b).



This is a known compound and has been fully characterised.[20a]

To a suspension of powdered molecular sieves (4 Å, 0.50 g) in dry methanol (30 cm^3) was added 4-(cyclohexa-1,4-dienyl)butanal **304** (265 mg, 1.76 mmol), (*R, R*)-TsDPEN **81** (712 mg, 1.94 mmol) and glacial acetic acid (4 drops). The reaction mixture was stirred at rt and monitored by TLC. After 2 hrs, the imine had formed (observed by TLC), and sodium cyanoborohydride (528 mg, 8.44 mmol) was added. The reaction was left to stir overnight at rt. Molecular sieves were removed by filtration, and the solution was concentrated under reduced pressure. The residue was re-dissolved in DCM (40 cm^3). The organic phase was washed with saturated $NaHCO_3$ (40 cm^3) and brine (40 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10→30 % v/v ethyl acetate/hexane) to afford **162b** as a white solid (265 mg, 0.53 mmol, 30 %); δ_H (400 MHz, $CDCl_3$) 7.37 (2 H, d, *J* 8.5, 2 x $NHSO_2Ar$-*o*-C*H*), 7.16-7.11 (3 H, m, 3 x Ar-*H*), 7.08-7.01 (5 H, m, 5 x Ar-*H*), 6.97-6.89 (4 H, m, 4 x Ar-*H*), 6.29 (1 H, br s, N*H*Ts), 5.74-5.67 (2 H, m, *H*C=C*H*), 5.35 (1 H, br s, C=C*H*), 4.24 (1 H, d, *J* 8.0, TsNHC*H*), 3.60 (1 H, d, *J* 8.0, NHC*H*), 2.72-2.65 (2 H, m, C=CCH_2C=C), 2.59-2.51 (2 H, m, C=CCH_2C=C), 2.43-2.35 (2 H, m, NHC$H_2$$CH_2CH_2$), 2.32 (3 H, s, TsC$H_3$), 1.90 (2 H, t, *J* 6.5, $NHCH_2CH_2CH_2CH_2$), 1.41-1.30 (5 H, m, $NHCH_2CH_2CH_2CH_2$ + N*H*); δ_C (101 MHz, $CDCl_3$) 142.69 (*C*), 139.40 (*C*), 138.41 (*C*), 137.09 (*C*), 134.70 (*C*), 129.09 (2 x *C*H), 128.30 (2 x *C*H), 127.90 (2 x *C*H), 127.59 (2 x *C*H), 127.44 (*C*H), 127.40 (2 x *C*H), 127.25 (*C*H), 127.15 (2 x *C*H), 124.35 (*C*H), 124.32 (*C*H), 118.49 (*C*H), 67.86 (*C*H), 63.08 (*C*H), 47.03 (CH_2), 37.20 (CH_2), 29.64 (CH_2), 28.87 (CH_2), 24.76 (CH_2), 23.44 (CH_2) and 21.44 (CH_3). The data matched that previously reported for this compound.

Synthesis of *N*-[(1*R*, 2*R*)-1,2-Diphenyl-2-(4-phenylbutylamino)-ethyl]-4-methylbenzenesulfonamide ammonium chloride ruthenium dimer (163b).

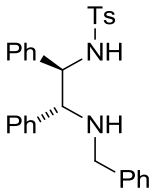


This is a known compound and has been fully characterised. [20a]

To a stirred solution of (*R*,*R*)-*N*-(4-cyclohexa-1,4-dienyl)butyl)-1,2-diphenyl-*N'*-tosylethane-diamine **162b** (265 mg, 0.53 mmol) in anhydrous DCM (8 cm^3) was added hydrochloric acid (2 M in diethyl ether, 0.80 cm^3, 1.59 mmol) at 0 °C. The reaction mixture was stirred at rt for 20 minutes, and subsequently concentrated under reduced pressure to give a white residue. To a suspension of the residue in ethanol (10 cm^3) was added ruthenium (III) trichloride hydrate (112 mg, 0.42 mmol). The reaction mixture was refluxed overnight. The precipitate was collected by filtration and washed with cold ethanol to give *N*-[(1*R*,2*R*)-1,2-diphenyl-2-(4-phenylbutylamino)-ethyl]-4-methylbenzenesulfonamide ammonium chloride ruthenium dimer **163b** (200 mg, 0.14 mmol, 54 %) as green-brown crystals; δ_H (400 MHz, DMSO-d_6) 9.47 (2 H, br s, 2 x $NH_{(1)}H_{(2)}^{+}Cl^{-}$), 9.02 (2 H, br s, 2 x $NH_{(1)}H_{(2)}^{+}Cl^{-}$), 8.60 (2 H, d, *J* 9.5, 2 x NHTs), 7.30-6.81 (28 H, m, 2 x (14 x Ar-*H*)), 6.02-5.72 (10 H, m, 2 x (5 x Ru-Ar-*H*)), 4.82 (2 H, m, 2 x PhC*H*NHTs), 4.58-4.51 (2 H, m, 2 x PhC*H*$NH_2^{+}Cl^{-}$), 2.74-2.66 (4 H, m, 2 x $NH_2^{+}Cl^{-}CH_2CH_2CH_2CH_2$), 2.45-2.39 (4 H, m, 2 x $CH_2NH_2^{+}Cl^{-}$), 2.21 (6 H, s, 2 x TsCH_3), 1.78-1.67 (4 H, m, 2 x $NH_2^{+}Cl^{-}CH_2CH_2CH_2CH_2$), 1.58-1.47 (4 H, m, 2 x $NH_2^{+}Cl^{-}CH_2CH_2CH_2CH_2$); δ_C (101 MHz, DMSO-d_6) 142.14 (2 x *C*), 137.67 (2 x *C*), 135.48 (2 x *C*), 131.49 (2 x *C*), 129.15 (2 x *C*H), 129.07 (2 x *C*H), 128.84 (2 x (2 x *C*H), 128.65 (2 x (2 x *C*H), 127.71 (2 x (2 x *C*H), 127.54 (2 x (2 x *C*H), 127.14 (2 x *C*H), 126.33 (2 x (3 x *C*H), 107.22 (2 x *C*), 88.87 (2 x (2 x *C*H), 84.84 (2 x *C*H), 84.82 (2 x *C*H), 83.09 (2 x *C*H), 64.29 (2 x *C*H), 60.58 (2 x *C*H), 45.25 (2 x CH_2), 31.72 (2 x CH_2),

25.58 (2 x CH_2), 24.38 (2 x CH_2) and 20.82 (2 x CH_3). The data matched that previously reported for this compound.

Synthesis of *N*-((1*R*, 2*R*)-2-(benzylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (305).

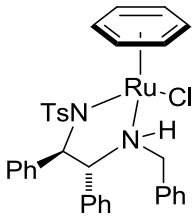


This is a known compound and has been fully characterised.[32a, 32b]

To a stirred solution of (*R*, *R*)-TsDPEN **81** (0.60 g, 1.64 mmol) and molecular sieves (4 Å, 2.0 g) in dried methanol (16 cm^3), was added benzaldehyde (0.20 cm^3, 1.96 mmol) followed by glacial acetic acid (6 drops). The reaction was followed by TLC until the imine was formed (3 hrs), and then sodium cyanoborohydride (0.30 g, 4.8 mmol) was added and the reaction was left overnight at rt. The molecular sieves were filtered through filter paper and the solution was then concentrated under reduced pressure to remove the methanol. The residue was dissolved in chloroform (100 cm^3), and was washed with saturated $NaHCO_3$ solution (60 cm^3). The organic layer was then dried ($MgSO_4$), filtered and concentrated under reduce pressure to give a crude solid which was purified by flash chromatography (10→30 % v/v ethyl acetate/hexane) to afford the product **305** as a while solid (430 mg, 0.94 mmol, 57 %); δ_H (400 MHz, $CDCl_3$) 7.36 (2 H, d, *J* 8.2, 2 x Ar-*H o* to SO_2NH), 7.32-7.22 (3 H, m, 3 x Ar-*H*), 7.19-7.12 (5 H, m, 5 x Ar-*H*), 7.09-6.88 (9 H, m, 9 x Ar-*H*), 6.13 (1 H, br s , N*H*Ts), 4.31 (1 H, dd, *J* 7.7, 2.9, C$H_{(1)}$H$_{(2)}$Ph), 3.68 (1 H, d, *J* 7.7, CH$_{(1)}H_{(2)}$Ph), 3.62 (1 H, d, *J* 13.2, TsNHC*H*), 3.41 (1 H, d, *J* 13.2, C*H*NH), 2.31 (3 H, s, CH_3Ts) and 1.68 (1 H, br s, N*H*CH_2Ph); δ_C (101 MHz, $CDCl_3$) 142.72 (*C*), 139.37 (*C*), 138.90 (*C*), 138.25 (*C*), 136.99 (*C*), 129.10 (2 x

*C*H), 128.48 (2 x *C*H), 128.43 (2 x *C*H), 128.04 (2 x *C*H), 127.95 (2 x *C*H), 127.62 (*C*H), 127.55 (2 x *C*H), 127.51 (2 x *C*H), 127.32 (*C*H), 127.18 (*C*H), 127.11 (2 x *C*H), 66.80 (*C*H), 63.09 (*C*H), 50.88 (CH_2) and 21.44 (CH_3). The data matched that previously reported for this compound.

Synthesis of NBn untethered catalyst (182).

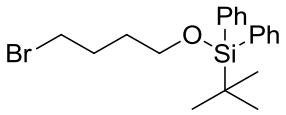


This is a known compound and has been fully characterised.[17j]

A mixture of benzeneruthenium(II) chloride dimer (0.16 g, 0.33 mmol), *N*-((1*R*, 2*R*)-2-(benzylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **305** (0.20 g, 0.44 mmol) and triethylamine (0.24 cm^3, 1.7 mmol) in IPA (10 cm^3) was heated at 80 °C for 1 hr. The solution was then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 cm^3) and then washed with water (10 cm^3) with vigorous stirring for 3 minutes. The organic phase was separated, dried (Na_2SO_4), filtered and then concentrated under reduced pressure giving the crude product, which was then purified by column chromatography (3: 3: 1 v/v/v ethyl acetate/ hexane/ methanol) providing **182** as a brown solid (189 mg, 0.28 mmol, 64 %); δ_H (400 MHz, $CDCl_3$) 7.40-6.50 (19 H, m, 19 x Ar-*H*), 5.60 (6 H, s, 6 x Ru-Ar-*H*), 4.50-4.40 (1 H, m, C*H*NTs), 4.29-4.20 (1 H, m, C*H*NH), 4.16 (1 H, d, *J* 10.7, $CH_{(1)}H_{(2)}$Ph), 3.93 (1 H, t, *J* 10.7, $CH_{(1)}H_{(2)}$Ph) and 2.24 (3 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 141.55 (*C*), 138.72 (*C*), 138.55 (*C*), 136.26 (*C*), 135.04 (*C*), 130.29 (2 x *C*H), 128.50 (2 x *C*H), 128.21 (3 x *C*H), 127.89 (2 x *C*H), 127.57 (*C*H), 127.40 (2 x *C*H), 127.11 (*C*H), 126.90 (*C*H),

126.71 (2 x *C*H), 126.22 (2 x *C*H), 125.66 (*C*H), 83.47 (6 x *C*H), 80.51 (*C*H), 68.96 (*C*H), 59.52 (CH_2) and 20.61 (CH_3). The data matched that previously reported for this compound.

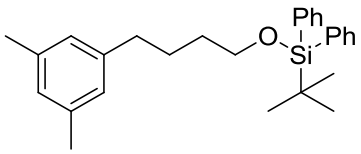
Synthesis of (4-bromobutoxy)(*tert*-butyl)diphenylsilane (185).



This is a known compound and has been fully characterised.[32c]

tert-Butyl-chlorodiphenylsilane (7.96 g, 7.53 cm^3, 28.97 mmol) was added to a stirred solution of 4-bromo-1-butanol (4.03 g, 26.34 mmol) and imidazole (3.95 g, 57.95 mmol) in THF (150 cm^3) under an argon atmosphere. The resulting mixture was stirred over the weekend at rt and quenched with water (150 cm^3) followed by the addition of Et_2O (150 cm^3). After phase separation and extraction of the aqueous phase with Et_2O (3 x 150 cm^3), the combined organic phases were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (0→10 % v/v ethyl acetate/hexane) to afford the silyl alcohol **185** as a colourless oil (3.23g, 8.25 mmol, 31%); δ_H (300 MHz, $CDCl_3$) 7.52-7.51 (4 H, m, 4 x Ar-*H*), 7.45-7.30 (6 H, m, 6 x Ar-*H*), 3.75 (2 H, t, *J* 6.1, CH_2OSi), 3.50 (2 H, t, *J* 6.8, BrCH_2), 2.06-1.93 (2 H, m, $BrCH_2CH_2$), 1.73-1.65 (2 H, m, CH_2CH_2OSi) and 1.09 (9 H, s, 3 x CH_3); δ_C (75 MHz, $CDCl_3$) 135.58 (*C*H), 133.84 (2 x *C*), 129.65 (3 x *C*H), 127.69 (6 x *C*H), 62.93 (CH_2), 33.91 (CH_2), 31.07 (CH_2), 29.48 (CH_2), 26.90 (3 x CH_3) and 19.24 (*C*). The data matched that previously reported for this compound.

Synthesis of *tert*-butyl(4-(3,5-dimethylphenyl)butoxy)diphenylsilane (187).

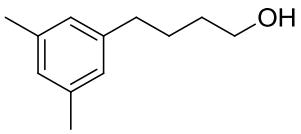


This compound is novel.

A Schlenk tube was dried with a heat gun under vacuum, and flushed with argon. 5-Bromo-m-xylene (1.53 g, 1.12 cm^3, 8.25 mmol) was injected into the tube followed by freshly distilled THF (16.5 cm^3). The tube was then degassed 3 times followed by the reinsertion of argon. ^{t}BuLi (1.7 M in pentane, 12.14 cm^3, 20.63 mmol) was added dropwise at -78 °C and the tube was again degassed and flushed with argon. The mixture was then stirred at room temperature for 1 hr, and then re-cooled to -78 °C. (4-Bromobutoxy)(*tert*-butyl)diphenylsilane (3.23 g, 8.25 mmol) was added dropwise to the reaction mixture and then degassed and flushed with argon. The solution was then heated up to 40 °C and allowed to stir at this temperature for 4 days. The mixture was then allowed to cool to room temperature and then was partitioned between diethyl ether (33 cm^3) and water (25 cm^3). The aqueous phase was extracted with Et_2O (2 x 16.5 cm^3), and then the combined organic phases were dried ($MgSO_4$), filtered and then evaporated *in vacuo* to give **187** as a light yellow oil (2.4 g, 5.76 mmol, 70 %); υ_{max} 3071, 2931, 2858, 1606, 1472, 1462, 1428, 1390, 1361, 1261, 1189, 1105, 1008, 998, 975, 939, 846, 822, 739 and 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.70-7.62 (3 H, m, 3 x Ar-*H*), 7.45-7.30 (7 H, m, 7 x Ar-*H*), 6.85 (1 H, s, Ar-*H*), 6.80 (2 H, s, 2 x Ar-*H*), 3.65 (2 H, t, *J* 6.2, C*H*$_2$OSi), 2.53 (2 H, t, *J* 7.8, ArC*H*$_2$), 2.25 (6 H, s, 2 x C*H*$_3$), 1.70 (2 H, m, ArCH$_2$C*H*$_2$), 1.60 (2 H, m, C*H*$_2$CH$_2$OSi) and 1.05 (9 H, s, 3 x SiCC*H*$_3$); δ_C (101 MHz, $CDCl_3$) 142.60 (*C*), 137.69 (2 x *C*), 135.60 (3 x *C*H), 134.12 (2 x *C*), 129.52 (2 x *C*H), 127.60 (5 x *C*H), 127.28 (*C*H), 126.28 (2 x *C*H), 63.76 (*C*H$_2$), 35.46 (*C*H$_2$), 32.25 (*C*H$_2$), 28.92 (*C*), 27.62 (*C*H$_2$), 26.89 (3 x *C*H$_3$) and 21.34 (2 x *C*H$_3$); *m/z* (ESI-MS)

439.0 $[M+Na]^+$. Found (ESI-HR-MS): 439.2419 $[M+Na]^+$, $C_{28}H_{36}NaOSi$ requires 439.2428 (1.86 ppm error).

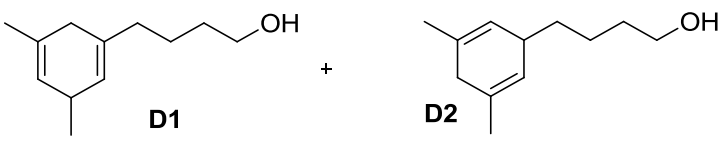
Synthesis of 4-(3,5-dimethylphenyl)butan-1-ol (188).



This compound is novel.

Tetrabutylammonium fluoride was added as a 1 M solution in THF (24 cm^3) to a solution of *tert*-butyl(4-(3,5-dimethylphenyl)butoxy)diphenylsilane (2.0 g, 4.8 mmol) in THF (65 cm^3). The mixture was allowed to stir for 3 days at 23 °C and the conversion was checked by TLC. After completion the solution was concentrated under reduced pressure and the crude product was purified by flash chromatography (10→50 % v/v ethyl acetate/hexane) to afford **188** as a colourless oil (776 mg, 4.35 mmol, 91 %); υ_{max} 3326, 3014, 2928, 2860, 1606, 1459, 1377, 1060, 1036, 985, 933, 894, 843 and 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.82 (1 H, s, Ar-*H*), 6.80 (2 H, s, 2 x Ar-*H*), 3.65 (2 H, t, *J* 6.2, C*H*$_2$OH), 2.59 (2 H, t, *J* 7.6, ArC*H*$_2$), 2.30 (6 H, s, 2 x C*H*$_3$) and 1.72-1.56 (4 H, m, C*H*$_2$C*H*$_2$CH$_2$OH); δ_C (101 MHz, $CDCl_3$) 142.28 (*C*), 137.77 (2 x *C*), 127.41 (*C*H), 126.27 (2 x *C*H), 62.91 (*C*H$_2$), 35.51 (*C*H$_2$), 32.46 (*C*H$_2$), 27.62 (*C*H$_2$) and 21.29 (2 x *C*H$_3$); *m/z* (ESI-MS) 201.1 $[M+Na]^+$. Found (ESI-HR-MS): 201.1247 $[M+Na]^+$, $C_{12}H_{18}NaO$ requires 201.1250 (1.5 ppm error)

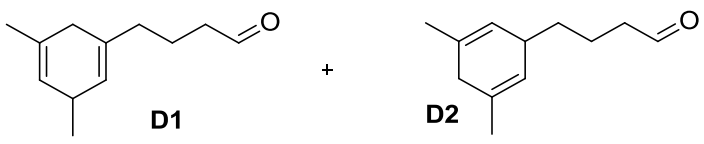
Synthesis of 4-(3,5-dimethylcyclohexa-1,4-dienyl)butan-1-ol (189).



This compound is novel.

A solution of 4-(3,5-dimethylphenyl)butan-1-ol (513 mg, 2.8 mmol) in ethanol (2.5 cm^3) was slowly added to a refluxing solution of ammonia (50 cm^3) containing ethanol (10 cm^3) at -78 °C while stirring. Small cleaned (with hexane) sodium pieces were added to the reaction mixture until the blue colour persisted. After the addition of sodium over the course of 7 hours with regular additions of ethanol (2.5 cm^3), the reaction mixture was left overnight to evaporate ammonia. The reaction mixture was quenched carefully with saturated ammonium chloride (20 cm^3), and extracted using DCM (3 x 6 cm^3). The combined organic layers were dried ($MgSO_4$) filtered and concentrated under reduced pressure to afford crude **189** as an orange red oil (374 mg, 3.07 mmol, 74%) which appeared to be a ca 1:1 mixture of isomers **D1** and **D2**. The product was analyzsed as a 1:1 mixture of **D1** and **D2**; δ_H (300 MHz, $CDCl_3$) 5.32 (2 H, br s, 2 x *H*C=C), 3.60-3.55 (2 H, m, CH_2OH), 2.71 (1 H, br s, O*H*), 2.45-2.40 (2 H, m, =C-CH_2-C=), 2.10-2.05 (1 H, m, =C-C*H*-C=), 1.65 (4.5 H, br s, CH_3), 1.50-1.20 (6 H, m, (CH_2)$_3$) and 0.95 (1.5 H, d, *J* 7.6, CHCH_3). **This material was directly used in the next step, and 90 % conversion was obtained after multiple reduction attempts on the same product.**

Synthesis of 4-(3,5-dimethylcyclohexa-1,4-dienyl)butanal (190).

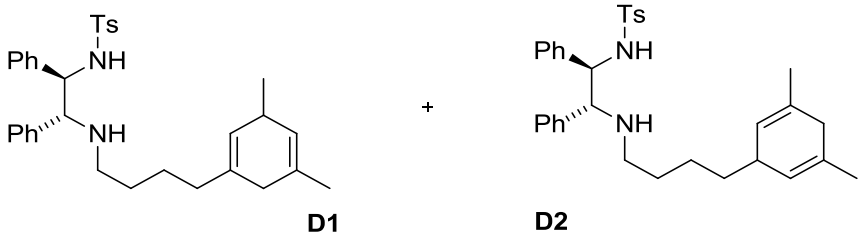


This compound is novel.

A solution of oxalylchloride (2 M in DCM, 1.35 cm^3, 2.69 mmol) in anhydrous DCM (3 cm^3) was cooled to -78 °C, and to this was slowly added a solution of dimethylsulfoxide

(0.38 cm^3, 5.38 mmol) in DCM (1.5 cm^3) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 4-(3,5-dimethylcyclohexa-1,4-dienyl)butan-1-ol (375 mg, 2.07 mmol) in DCM (5 cm^3) was slowly added at the same temperature. After stirring for 45 minutes at -78 °C, Et_3N (1.73 cm^3, 12.40 mmol) was added and the reaction mixture was allowed to warm up to rt. After 60 minutes, water (10 cm^3) was added, and the mixture was extracted with DCM (3 x 5 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give crude **190** as a light orange oil (355 mg, 1.99 mmol, 96 %) which appeared to be a ca. 1:1 mixture of isomers **D1** and **D2**. The product was analyzsed as a 1:1 mixture of **D1** and **D2**; δ_H (400 MHz, $CDCl_3$) 9.88 (0.5 H, s, C*H*=O), 9.85 (0.5 H, s, C*H*=O)**,** 5.30-5.20 (2 H, m, -C*H*=), 2.35-2.30 (4 H, m, =C-CH_2-C=), 2.05-2.00 (0.5 H, m, =C-C*H*-C=), 1.80-1.70 (0.5 H, m, =C-C*H*-C=), 1.68 (4.5 H, br s, CH_3), 1.65-1.55 (2 H, m, CH_2), 1.40-1.30 (2 H, m, CH_2), 1.00 (1.5 H, d, *J* 7.7, CH_3); **This material was directly used in the next step.**

Synthesis of *N*-((1*R*,2*R*)-2-(4-(3,5-dimethylcyclohexa-1,4-dienyl)butylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (191).

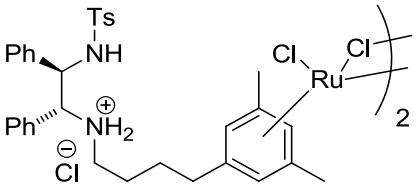


This compound is novel.

To a suspension of powdered molecular sieves (4 Å, 0.50 g) in dry methanol (30 cm^3) was added 4-(3,5-dimethylcyclohexa-1,4-dienyl)butanal **190** (355 mg, 2.00 mmol), (*R*, *R*)-TsDPEN (806 mg, 2.20 mmol) and glacial acetic acid (4 drops). The reaction

mixture was stirred at rt and monitored by TLC. After 2 hrs, the imine had formed (observed by TLC), and sodium cyanoborohydride (590 mg, 9.38 mmol) was added. The reaction was left overnight at rt The molecular sieves were then removed by filtration, and the solution was concentrated under reduced pressure. The residue was redissolved in DCM (40 cm^3). The organic phase was washed with saturated $NaHCO_3$ (40 cm^3) and brine (40 cm^3), dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by flash chromatography (10→30 % v/v ethyl acetate/hexane) to afford **191** as a colourless oil (390 mg, 0.74 mmol, 37 %) which appeared to be a ca. 1:1 mixture of isomers **D1** and **D2**. The product was analyzsed as a 1:1 mixture of **D1** and **D2**; $[\alpha]_D^{35}$ -5.3 (c 0.5, $CHCl_3$); υ_{max} 3299, 3030, 2926, 2856, 2257, 1600, 1495, 1455, 1433, 1380, 1352, 1327, 1305, 1184, 1160, 1119, 1093, 1054, 1020, 909, 846, 807, 755, 731, 698 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37 (2 H, d, *J* 8.2, 2 x Ar-*H*), 7.15-7.10 (3 H, m, 3 x Ar-*H*), 7.05-7.00 (5 H, m, 5 x Ar-*H*), 6.95-6.85 (4 H, m, 4 x Ar-*H*), 5.35-5.25 (2 H, br s, *H*C=C), 4.26-4.21 (1 H, m, C*H*Ts), 3.62-3.57 (1 H, m, C*H*NH), 2.80-2.59 (1 H, m, CH_3CH), 2.43-2.36 (2 H, m, $CH_2C(CH_3)$=C), 2.35 (3 H, s, TsCH_3)**,** 2.34-2.25 (2 H, m, NHCH_2), 1.70 (4.5 H, s, CH_3), 1.56-1.14 (6 H, m, $NHCH_2CH_2CH_2CH_2$) and 1.05 (1.5 H, d, *J* 7.2, CH_3); δ_C (101 MHz, $CDCl_3$) 142.67 (*C*), 139.43 (*C*), 138.42 (*C*), 137.09 (*C*), 131.05 (2 x *C*), 129.08 (2 x *C*H), 128.30 (2 x *C*H), 127.90 (2 x *C*H), 127.58 (2 x *C*H), 127.43 (*C*H), 127.39 (2 x *C*H), 127.25 (*C*H), 127.15 (2 x *C*H), 125.18 (*C*H), 124.98 (*C*H), 123.40 (*C*H), 67.86 (*C*H), 63.06 (*C*H), 47.20 (CH_2), 36.12 (CH_2), 34.02 (CH_2), 30.35 (CH_2), 29.63 (CH_2), 23.09 (CH_3) and 21.44 (2 x CH_3); *m/z* (ESI-MS) 529.3 $[M+H]^+$. Found (ESI-HR-MS): 529.2899 $[M+H]^+$, $C_{33}H_{41}N_2O_2S$ requires 529.2883 (-2.9 ppm error).

Synthesis of *N*-((1*R*,2*R*)-2-(4-(3,5-dimethylphenyl)butylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide ammonium chloride dimer (183).



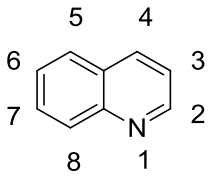
This compound is novel.

To a stirred solution of *N*-((1*R*,2*R*)-2-(4-(3,5-dimethylcyclohexa-1,4-dienyl)butylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **191** (200 mg, 0.38 mmol) in anhydrous DCM (5.5 cm^3) was added hydrochloric acid (2 M in diethyl ether, 0.57 cm^3, 1.14 mmol) at 0 °C. The reaction mixture was stirred at rt for 20 minutes, and subsequently concentrated under reduced pressure to give a white residue. To a suspension of the residue in ethanol (7.2 cm^3) was added hydrate ruthenium (III) trichloride hydrate (62 mg, 0.30 mmol). The reaction mixture was refluxed overnight. The precipitate was collected by filtration and washed with ethanol to give **183** (54 mg, 0.04 mmol, 21 %) as black crystals; Mp 240-250°C (dec.); υ_{max} 3054, 1597, 1456, 1323, 1156, 1091, 1030, 925, 813, 763, 700 and 669 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 9.36 (2 H, br s, 2 x N*H*$_{(1)}$H$_{(2)}^+$Cl$^-$), 8.95 (2 H, br s, 2 x NH$_{(1)}$*H*$_{(2)}^+$Cl$^-$), 8.50 (2 H, br s, 2 x N*H*Ts), 7.33-6.70 (28 H, m, 2 x (14 x Ar-*H*)), 5-55.5.50 (6 H, m, 2 x (3 x Ru-Ar-*H*)), 4.74-4.66 (2 H, m, 2 x C*H*NHTs)), 4.50-4.40 (2 H, m, 2 x C*H*NH$_2^+$), 2.80-2.70 (4 H, m, 2 x NH$_2^+$C*H*$_2$), 2.55 (12 H, br s, 2 x (2 x C*H*$_3$)), 2.40-2.35 (4 H, m, 2 x C*H*$_2$Ar), 2.20 (6 H, s, SO$_2$ArC*H*$_3$), 1.83-1.50 (8 H, m, 2 x (2 x CH$_2$)); δ_C (101 MHz, DMSO-d_6) 142.24 (2 x *C*), 137.50 (2 x *C*), 135.35 (2 x *C*), 131.41 (2 x *C*), 129.22 (2 x CH), 129.07 (2 x (2 x *C*H)), 128.92 (2 x (2 x *C*H)), 128.70 (2 x (2 x *C*H)), 127.70 (2 x (2 x *C*H)), 127.57 (2 x (2 x *C*H)), 127.19 (2 x *C*H), 126.38 (2 x (2 x *C*H)), 107.10 (2 x *C*), 104.11 (2 x (2 x *C*)), 82.80 (2 x *C*H), 82.16 (2 x *C*H), 82.11 (2 x *C*H), 64.37 (2 x *C*H), 60.49 (2 x *C*H), 45.40 (2 x *C*H$_2$), 31.55 (2 x *C*H$_2$), 26.12 (2 x *C*H$_2$), 24.51 (2 x *C*H$_2$), 20.90 (2 x *C*H$_3$)

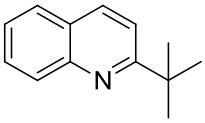
and 18.30 (2 x (2 x *C*H_3); *m/z* 1321, 1307, 627 (0.5M-2HCl-Cl), 353 (Molecular ion not observed; fragmentation ions with Ru isotope patterns observed). Found (ESI-HR-MS): 627.1631 $C_{33}H_{37}N_2O_2{}^{102}RuS$ (monomer formed *in situ* from dimer) requires 627.1622 (1.4 ppm error), 314.0841, $C_{33}H_{38}N_2O_2{}^{102}RuS(2+)$ requires 314.0847 (1.9 ppm error). **Optical rotation could not be obtained due to the product being highly coloured.**

General procedure for making quinolines.

2-Methylquinoline and 2-phenylquinoline were purchased from Sigma-Aldrich and Alfa Aesar.



Synthesis of 2-*tert*-butylquinoline (178).

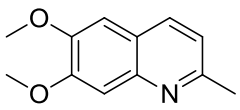


This is a known compound and has been fully characterised.[26b]

To a solution of 6-nitrobenzaldehyde (3.02 g, 20 mmol) in ethanol (60 cm^3) was added iron power (<10 μm, aldrich, 4.47 g, 80 mmol) followed by 0.1 N aq HCl (10 cm^3, 1 mmol) and the resulting mixture was vigorously stirred at 95 °C (oil bath) for 2 hrs. TLC analysis revealed that the reduction reaction was complete so 3,3-dimethyl-2-butanone (2.0 g, 2.5 cm^3, 20 mmol) and powdered KOH (1.35 g, 24 mmol) were added successively in portions (Caution! Potential exotherm; add KOH slowly). The reaction mixture was stirred at 95 °C, then cooled to rt, diluted with DCM (600 cm^3), and filtered through a celite pad. The filtrate was washed with water (100 cm^3) and the aqueous

phase was back-extracted with DCM (2 x 40 cm^3). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give **178** as an orange red oil (3.7 g, 20 mmol,>99 %); δ_H (400 MHz, $CDCl_3$) 8.08-8.01 (2 H, m, (4)-C*H* + (8)-C*H*), 7.73 (1 H, d, *J* 7.0, (5)-C*H*), 7.65 (1 H, t, *J* 7.0, (7)-C*H*), 7.50 (1 H, d, *J* 8.6, (3)-C*H*), 7.45 (1 H, t, *J* 7.0, (6)-C*H*) and 1.49 (9 H, s, (2)-3 x CH_3); δ_C (101 MHz, $CDCl_3$) 169.28 (*C*), 147.47 (*C*), 135.86 (*C*H), 129.45 (*C*H), 128.99 (CH), 127.24 (CH), 126.47 (*C*), 125.63 (*C*H), 118.24 (*C*H), 38.16 (*C*) and 30.18 (3 x *C*H_3). The data matched that previously reported for this compound.

Synthesis of 6,7-dimethoxy-2-methylquinoline (193).

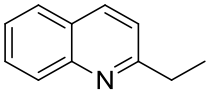


This is a known compound and has been fully characterised.[32d]

To a solution of 6-nitroveratraldehyde (2.11 g, 10 mmol) in ethanol (30 cm^3) was added iron power (<10μm, aldrich, 2.23 g, 40 mmol) followed by 0.1 N aq HCl (5 cm^3, 0.5 mmol) and the resulting mixture was vigorously stirred at 95 °C (oil bath) for 2 hrs. TLC analysis revealed that the reduction reaction was complete so acetone (0.58 g, 0.73 cm^3, 10 mmol) and powdered KOH (0.67 g, 12 mmol) were added successively in portions (Caution! Potential exotherm; add KOH slowly). The reaction mixture was stirred at 95 °C, then cooled to rt, diluted with DCM (300 cm^3), and filtered through a celite pad. The filtrate was washed with water (50 cm^3) and the aqueous phase was back-extracted with DCM (2 x 20 cm^3). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give **193** as brown crystals (1.55 g, 7.63 mmol, 76 %); δ_H (400 MHz, $CDCl_3$) 7.88 (1 H, d, *J* 8.3, (4)-C*H*), 7.38 (1 H, s, (8)-C*H*), 7.10 (1 H, d, *J* 8.3, (3)-C*H*), 6.95 (1 H, s, (5)-C*H*), 4.01 (3 H, s, (7)-OCH_3), 3.99 (3 H, s,

(6)-OC*H*$_3$) and 2.70 (3 H, s, (2)-C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 156.53 (*C*), 152.30 (*C*), 149.06 (*C*), 144.75 (*C*), 134.46 (*C*H), 121.70 (*C*), 120.08 (*C*H), 107.54 (*C*H), 105.09 (*C*H), 56.05 (*C*H$_3$), 55.95 (*C*H$_3$) and 24.97 (*C*H$_3$). The data matched that previously reported for this compound.

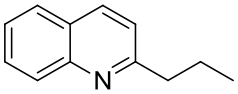
Synthesis of 2-ethylquinoline (120b).



This is a known compound and has been fully characterised.[32e]

Quinaldine (1.40 g, 1.4 cm^3,10 mmol) was dissolved in dry THF (20 cm^3). The reaction vessel was cooled to -78 °C and ^{n}BuLi in hexane (1.6 M, 6.3 cm^3, 10 mmol) was added. After 30 mins, methyl iodide (1.90 g, 0.8 cm^3, 13 mmol) was added via syringe. The mixture was allowed to gradually warm to room temperature while being stirred overnight. The resulting light yellow solution was concentrated, diluted with water (40 cm^3) and brine (10 cm^3), and extracted with DCM (3 x 40 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give **120b** as an yellow oil (1.46 g, 9.29 mmol, 93 %); δ_H (400 MHz, $CDCl_3$) 8.05 (1 H, d, *J* 8.5, (8)-C*H*), 7.99 (1 H, d, *J* 8.5, (4)-C*H*), 7.70 (1 H, d, *J* 8.5, (5)-C*H*), 7.61 (1 H, t, *J* 7.0, (7)-C*H*), 7.39 (1 H, t, *J* 7.0, (6)-C*H*), 7.25 (1 H, d, *J* 8.5, (3)-C*H*), 2.88 (2 H, q, *J* 7.7, (2)-C*H*$_2$CH$_3$) and 1.30 (3 H, t, *J* 7.7 Hz, (2)-CH$_2$C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 163.95 (*C*), 147.88 (*C*), 136.30 (*C*H), 129.31 (*C*H), 128.81 (*C*H), 127.47 (*C*H), 126.72 (*C*), 125.63 (*C*H), 120.82 (*C*H), 32.32 (*C*H$_2$) and 14.50 (*C*H$_3$). The data matched that previously reported for this compound.

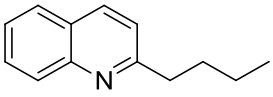
Synthesis of 2-propylquinoline (124a).



This is a known compound and has been fully characterised.[32f]

This compound was prepared as for 2-ethylquinoline using quinaldine (1.40 g, 1.4 cm^3, 10 mmol), ^{n}BuLi in hexane (1.6 M, 6.3 cm^3, 10 mmol) and ethyliodide (2.0 g, 1.0 cm^3, 13 mmol) and was isolated as a yellow oil (1.53 g, 8.93 mmol, 89 %); δ_H (400 MHz, $CDCl_3$) 8.05 (1 H, d, *J* 8.5, (8)-C*H*), 7.96 (1 H, d, *J* 8.4, (4)-C*H*), 7.78 (1 H, d, *J* 8.4, (5)-C*H*), 7.68 (1 H, t, *J* 7.0, (7)-C*H*), 7.49 (1 H, t , *J* 7.0, (6)-C*H*), 7.25 (1 H, d, *J* 8.4, (3)-C*H*), 2.99 (2 H, t, *J* 7.4, (2)-C$H_2$$CH_2CH_3$), 1.90 (2 H, sext, *J* 7.4, (2)-CH_2C$H_2$$CH_3$) and 1.05 (3 H, t, *J* 7.4, (2)-CH_2CH_2CH_3); δ_C (101 MHz, $CDCl_3$) 162.80 (*C*), 147.92 (*C*), 136.08 (*C*H), 129.25 (*C*H), 128.82 (*C*H), 127.45 (*C*H), 126.70 (*C*), 125.59 (*C*H), 121.33 (*C*H), 41.26 (CH_2), 23.24 (CH_2) and 14.00 (CH_3). The data matched that previously reported for this compound.

Synthesis of 2-butylquinoline (115l).

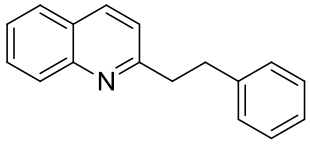


This is a known compound and has been fully characterised.[32g]

This compound was prepared as for 2-ethylquinoline using quinaldine (1.40 g, 1.4 cm^3, 10 mmol), ^{n}BuLi in hexane (1.6 M, 6.3 cm^3, 10 mmol) and iodopropane (2.21 g, 1.27 cm^3, 13 mmol) and was isolated as a yellow oil (1.70 g, 9.18 mmol, 92 %); δ_H (400 MHz, $CDCl_3$) 8.06 (1 H, d, *J* 8.5, (8)-C*H*), 7.99 (1 H, d, *J* 8.4, (4)-C*H*), 7.71 (1 H, d, *J* 8.4, (5)-C*H*), 7.64 (1 H, t, *J* 7.0, (7)-C*H*), 7.43 (1 H, t, *J* 7.0, (6)-C*H*), 7.23 (1 H, d, *J* 8.4, (3)-C*H*), 2.98 (2 H, dd, *J* 7.6, 8.0, (2)-C$H_2$$CH_2CH_2CH_3$), 1.83 (2 H, quin, *J* 7.6, (2)-CH_2C$H_2$$CH_2CH_3$), 1.43 (2 H, sext, *J* 7.6, (2)-CH_2CH_2C$H_2$$CH_3$) and 0.95 (3 H, t, *J* 7.6,

(2)-$CH_2CH_2CH_2CH_3$); δ_C (101 MHz, $CDCl_3$) 163.05 (*C*), 147.94 (*C*), 136.11 (*C*H), 129.27 (*C*H), 128.84 (2 x *C*H), 126.70 (*C*), 125.59 (*C*H), 121.34 (*C*H), 39.10 (CH_2), 32.17 (CH_2), 22.69 (CH_2) and 14.00 (CH_3). The data matched that previously reported for this compound.

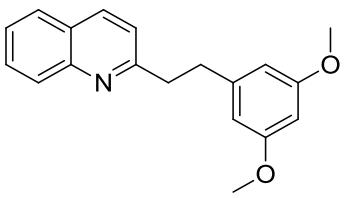
Synthesis of 2-phenylethylquinoline (117a).



This is a known compound and has been fully characterised.[32h]

This compound was prepared as for 2-ethylquinoline using quinaldine (1.40 g, 1.4 cm^3, 10 mmol), ^{n}BuLi in hexane (2.5 M, 4.0 cm^3, 10 mmol) and benzyl bromide (2.22 g, 1.55 cm^3, 13 mmol) and was isolated as a yellow oil (1.90 g, 8.14 mmol, 81 %); δ_H (400 MHz, $CDCl_3$) 8.23 (1 H, d, *J* 8.4, (8)-C*H*), 7.97 (1 H, d, *J* 8.4, (4)-C*H*), 7.77-7.69 (2 H, m, (5)-C*H* + (7)-C*H*), 7.49 (1 H, t, *J* 7.8, (6)-C*H*), 7.38-7.23 (5 H, m, (2)-$CH_2CH_2C_6H_5$), 7.18 (1 H, d, *J* 8.4, (3)-C*H*), 3.36 (2 H, dd, *J* 10.1, 9.2, (2)-$CH_2CH_2C_6H_5$) and 3.24 (2 H, dd, *J* 10.1, 9.2, (2)-$CH_2CH_2C_6H_5$); δ_C (101 MHz, $CDCl_3$) 161.81 (*C*), 148.12 (*C*), 141.63 (*C*), 136.24 (*C*H), 129.01 (*C*H), 128.64 (3 x *C*H), 128.55 (3 x *C*H), 126.89 (*C*), 126.15 (*C*H), 125.88 (*C*H) 121.63 (*C*H), 41.05 (CH_2) and 35.98 (CH_2). The data matched that previously reported for this compound.

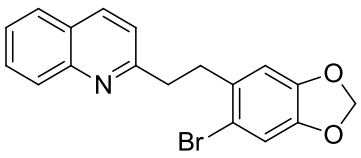
Synthesis of 2-(3,5-dimethoxyphenethyl)quinoline (195).



This compound is novel.

This compound was prepared as for 2-ethylquinoline using quinaldine (1.40 g, 1.4 cm^3, 10 mmol), ^{n}BuLi in hexane (1.6 M, 6.3 cm^3, 10 mmol) and 3,5-dimethoxybenzyl bromide (3.0 g, 13 mmol) and was isolated as an orange oil (2.29 g, 7.8 mmol, 78 %); υ_{max} 3057, 2998, 2935, 2837, 1735, 1594, 1563, 1504, 1459, 1427, 1349, 1310, 1295, 1204, 1147, 1115, 1065, 826, 750 and 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.10-8.02 (2 H, (8)-C*H* + (4)-C*H*), 7.77 (1 H, dd, *J* 8.1, 1.5, (5)-C*H*), 7.69 (1 H, dd, *J* 15.3, 1.5, (7)-C*H*), 7.49 (1 H, dd, *J* 15.3, 1.5, (6)-C*H*), 7.24 (1 H, d, *J* 8.5, (3)-C*H*), 6.43 (2 H, d, *J* 2.3, (2)-CH_2CH_2Ar(*o*-C*H*'s)), 6.32 (1 H, t, *J* 2.3, (2)-CH_2CH_2Ar(*p*-C*H*)), 3.74 (6 H, s, (2)-CH_2CH_2Ar(*m*-OCH_3's)), 3.31-3.26 (2 H, m, (2)-CH_2CH_2Ar) and 3.12-3.07 (2 H, m, (2)-CH_2CH_2Ar); δ_C (75 MHz, $CDCl_3$) 161.12 (*C*), 160.16 (2 x *C*), 147.36 (*C*), 143.32 (*C*), 135.64 (*C*H), 128.81 (*C*H), 128.23 (*C*H), 126.93 (*C*H), 126.20 (*C*), 125.21 (*C*H), 120.98 (*C*H), 105.90 (2 x *C*H), 97.56 (*C*H), 54.63 (2 x *C*H_3), 40.21 (*C*H_2) and 35.64 (*C*H_2); *m/z* (ESI-MS) 294.0 $[M+H]^+$. Found (ESI-HR-MS): 294.1486 $[M+H]^+$, $C_{19}H_{20}NO_2$ requires 294.1489 (1.0 ppm error).

Synthesis of 2-(2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)ethyl)quinoline (194).

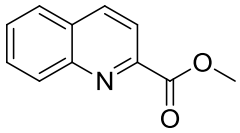


This is a known compound and has been fully characterised.[26g]

This compound was prepared as for 2-ethylquinoline using quinaldine (1.40 g, 1.4 cm^3, 10 mmol), ^{n}BuLi in hexane (1.6 M, 6.3 cm^3, 10 mmol) and 5-bromo-6-bromomethyl-1,3-benzodioxole (3.8 g, 13 mmol) and was isolated as white crystals (1.65 g, 4.63 mmol, 46 %); δ_H (300 MHz, $CDCl_3$) 8.08-8.00 (2 H, m, (8)-C*H* + (4)-C*H*), 7.77 (1 H,

dd, *J* 1.5, 8.3, (5)-C*H*), 7.68 (1 H, dd, *J* 15.3, 1.5, (7)-C*H*), 7.48 (1 H, dd, *J* 15.3, 1.5, (6)-C*H*), 7.27 (1 H, d, *J* 8.3, (3)-C*H*), 7.00 (1 H, s, (2)-CH_2CH_2Ar(*m*-C*H*)), 6.72 (1 H, s, (2)-CH_2CH_2Ar(*o*-C*H*)), 5.91 (2 H, s, (2)-CH_2CH_2Ar(O_2CH_2)) and 3.24-3.15 (4 H, m, (2)-CH_2CH_2Ar); δ_C (75 MHz, $CDCl_3$) 160.75 (*C*), 147.34 (*C*), 146.69 (*C*), 146.15 (*C*), 135.70 (*C*H), 133.15 (*C*), 128.81 (*C*H), 128.27 (*C*H), 126.93 (*C*H), 126.23 (*C*), 125.23 (*C*H), 120.95 (*C*H), 113.79 (*C*), 112.10 (*C*H), 109.57 (*C*H), 100.93 (CH_2), 38.72 (CH_2) and 35.53 (CH_2). The data matched that previously reported for this compound.

Synthesis of methyl quinoline-2-carboxylate (179).



This is a known compound and has been fully characterised.[32i]

To a suspension of quinaldic acid (1.73 g, 10.00 mmol) in MeOH (20 cm^3) was added a solution of HCl in MeOH (1.25 M, 20 cm^3). The resulting solution was refluxed for 15 hrs. The mixture was then cooled to rt and concentrated *in vacuo*. The residue was partitioned between saturated aqueous $NaHCO_3$ solution (25 cm^3) and EtOAc (3 x 20 cm^3). The combined organic extracts were further washed with saturated aqueous $NaHCO_3$ solution (7 cm^3) and water (7 cm^3), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give **179** as a white solid (1.43 g, 7.64 mmol, 76 %); δ_H (400 MHz, $CDCl_3$) 8.35-8.26 (2 H, m, (4)-C*H* + (8)-C*H*), 8.21 (1 H, d, *J* 8.4, (5)-C*H*), 7.89 (1 H, d, *J* 8.4, (3)-C*H*), 7.80 (1 H, t, *J* 7.4, (7)-C*H*), 7.66 (1 H, t, *J* 7.4, (6)-C*H*) and 4.09 (3 H, s, OCH_3); δ_C (101 MHz, $CDCl_3$) 166.00 (*C*=O), 147.92 (*C*), 147.56 (*C*), 137.35 (*C*H), 130.74 (*C*H), 130.33 (*C*H), 129.38 (*C*), 128.66 (*C*H), 127.58 (*C*H), 121.06 (*C*H) and 53.24 (CH_3). The data matched that previously reported for this compound.

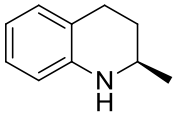
General procedure for the ATH of Quinolines.[22]

A solution of ruthenium dimer (0.0025 mmol) and imine (1 mmol) in methanol (1.6 cm^3) was stirred in a flame dried Schlenk tube at 28 °C for 10 minutes. Formic acid / triethylamine (5:2) azeotrope (0.5 cm^3) was then added (The Schlenk tube was degassed and purged with argon 3x before and after the addition of reagents). The reaction mixture was stirred at 28°C and monitored by TLC or GC, for which a drop of sample was filtered through a small plug of silica in a glass pipette using ethyl acetate and maybe a few drops of methanol depending on the polarity of the compound. After completion, $NaHCO_3$ solution (5 cm^3) was added, and the mixture was extracted with dichloromethane (3 x 10 cm^3). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the desired amine.

General procedure for formation of the racemic mixture.[10b]

To reaction vessel (A) was added $[Ru(p\text{-cymene})Cl_2]_2$ (0.0028 g, 0.0045 mmol) and undistilled THF (2 cm^3). The mixture was stirred until the solution was homogeneous. At the same time, to reaction vessel (B) was added quinoline (0.13 g, 0.12 cm^3, 0.89 mmol) and I_2 (0.012 g, 0.045 mmol), followed by THF (1 cm^3). The mixture was stirred until the iodine was dissolved. Then to the reaction bottle (B) was added the solution of $[Ru(p\text{-cymene})Cl_2]_2$ in THF from vessel (A). The final mixture in a glass vessel was pressurised to 600 psi hydrogen in a pressure hydrogenator and stirred at 20 °C for 20 hrs. The reaction mixture was concentrated to afford the crude product, which was then filtered through silica before being used for enantiomeric excess analysis on the GC/HPLC.

(*R*)-2-Methyl-1,2,3,4-tetrahydroquinoline (120a').

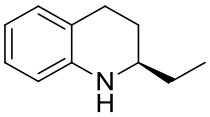


This is a known compound and has been fully characterised.[10h]

Reduction of **120a** using catalyst **163b**; 46% ee and 96% conversion, reduction of **120a** using catalyst **175;** 93% ee and 68% conversion: Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 125°C, P = 15 psi, He, imine 43.9 min., *S* isomer 67.5 min (minor),. *R* isomer 68.6 min (major)); *$[\alpha]_D^{27}$ +46.7 (*c* 0.5, $CHCl_3$) 43% ee (*R*) (lit.[10h] $[\alpha]_D^{25}$ -78.3 (*c* 0.76, $CHCl_3$) 91% ee (*S*)); δ_H (300 MHz, $CDCl_3$) 6.98-6.95 (2 H, m, (7)-C*H* + (5)-C*H*), 6.61 (1 H, td, *J* 7.2, 1.2, (6)-C*H*), 6.48 (1 H, dd, *J* 8.1, 1.3, (8)-C*H*), 3.70 (1 H, br s, (1)-N*H*), 3.44-3.38 (1 H, m, (2)-C*H*), 2.85-2.74 (2 H, m, (4)-CH_2), 1.94-1.91 (1 H, m, (3)-C*H*), 1.64-1.55 (1 H, m, (3)-C*H*) and 1.22 (3 H, d, *J* 6.3, (2)-CHCH_3); δ_C (75 MHz, $CDCl_3$) 144.20 (*C*), 128.67 (*C*H), 126.09 (*C*H), 120.50 (*C*), 116.37 (*C*H), 113.40 (*C*H), 46.56 (*C*H), 29.50 (CH_2), 26.00 (CH_2) and 22.02 (CH_3). The data matched that previously reported for this compound.

*$[\alpha]_D$ determined on sample with 43% ee.

(*R*)-2-Ethyl-1,2,3,4-tetrahydroquinoline (120b').



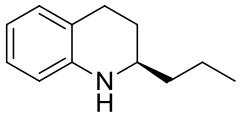
This is a known compound and has been fully characterised.[10h]

Reduction of **120b** using catalyst **163b**; 41% ee and 95% conversion: Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 115°C, P = 15 psi, He, imine 94.6 min., *S* isomer 174.0 min (minor)., *R* isomer 176.4 min (major)); $[\alpha]_D^{28}$ +35.6 (*c* 0.5, $CHCl_3$) 41% ee (*R*) (lit.[10h] $[\alpha]_D^{25}$ -73.2 (*c* 0.24, $CHCl_3$)

91% ee (*S*)); δ_H (300 MHz, $CDCl_3$) 6.98-6.94 (2 H, m, (7)-C*H* + (5)-C*H*), 6.60 (1 H, td, *J* 7.2, 1.2, (6)-C*H*), 6.47 (1 H, dd, *J* 8.4, 1.3, (8)-C*H*), 3.77 (1 H, br s, (2)-N*H*), 3.19-3.13 (1 H, m, (2)-C*H*), 2.85-2.69 (2 H, m, (4)-CH_2), 2.00-1.94 (1 H, m, (3)-C*H*), 1.63-1.48 (3 H, m, (3)-C*H* + (2)-CHC$H_2$$CH_3$) and 0.98 (3 H, t, *J* 7.5, (2)-CHCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 144.77 (*C*), 129.27 (*C*H), 126.73 (*C*H), 121.43 (*C*), 116.89 (*C*H), 114.02 (*C*H), 52.06 (*C*H), 29.44 (*C*H_2), 27.61 (*C*H_2), 26.45 (*C*H_2) and 10.12 (*C*H_3). The data matched that previously reported for this compound.

Reduction of **120b** using catalyst **175**; 91% ee and 67% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 17.0°C): t_R = 26.8 min (major), t_S = 30.5 (minor).

(*R*)-2-Propyl-1,2,3,4-tetrahydroquinoline (124a').



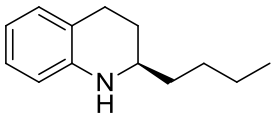
This is a known compound and has been fully characterised.[12b]

Reduction of **124a** using catalyst **163b**; 42% ee and 94% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 18.0°C): t_R = 23.6 min (major), t_S = 26.8 (minor); $[\alpha]_D^{24}$ +54.1 (*c* 0.5, $CHCl_3$) 42% ee (*R*) (lit.[12b] $[\alpha]_D^{21}$ -70.8 (*c* 1.1, $CHCl_3$) 80% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 6.97-6.94 (2 H, m, (7)-C*H* + (5)-C*H*), 6.59 (1 H, t, *J* 7.3, (6)-C*H*), 6.47 (1 H, d, *J* 8.0, (8)-C*H*), 3.76 (1 H, br s, (1)-N*H*), 3.28-3.21 (1 H, m, (2)-C*H*), 2.85-2.69 (2 H, m, (4)-CH_2), 1.98-1.92 (1 H, m, (3)-C*H*), 1.64-1.54 (1 H, m, (3)-C*H*), 1.51-1.39 (4 H, m, (2)-CHCH_2C$H_2$$CH_3$) and 0.96 (3 H, t, *J* 6.6,

(2)-CHCH$_2$CH$_2$C*H$_3$)*; δ_C (101 MHz, $CDCl_3$) 144.77 (*C*), 129.29 (*C*H), 126.73 (*C*H), 121.42 (*C*), 116.91 (*C*H), 114.06 (*C*H), 51.33 (*C*H), 38.93 (*C*H$_2$), 28.15 (*C*H$_2$), 26.47 (*C*H$_2$), 19.00 (*C*H$_2$) and 14.30 (*C*H$_3$). The data matched that previously reported for this compound.

Reduction of **124a** using catalyst **175**; 90% ee and 65% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 14.5°C): t_R = 24.5 min (major), t_S = 28.1 (minor).

(*R*)-2-Butyl-1,2,3,4-tetrahydroquinoline (115l').



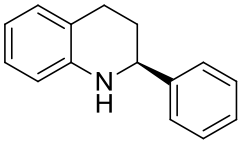
This is a known compound and has been fully characterised.[10h]

Reduction of **115l** using catalyst **163b**; 41% ee and 93% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 18.5°C): t_R = 21.8 min (major), t_S = 24.4 (minor); $[\alpha]_D^{26}$ +46.6 (*c* 0.5, $CHCl_3$) 41% ee (*R*) (lit.[10h] $[\alpha]_D^{25}$ -78.2 (*c* 0.53, $CHCl_3$) 89% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 6.96-6.93 (2 H, m, (7)-C*H* + (5)-C*H*), 6.59 (1 H, t, *J* 7.4, (6)-C*H*), 6.46 (1 H, d, *J* 8.3, (8)-C*H*), 3.72 (1 H, br s, (1)-N*H*), 3.24-3.18 (1 H, m, (2)-C*H*), 2.84-2.68 (2 H, m, (4)-C*H$_2$*), 1.98-1.91 (1 H, m, (3)-C*H*), 1.63-1.53 (1 H, m, (3)-C*H*), 1.51-1.45 (2 H, m, (2)-CHC*H$_2$*CH$_2$CH$_2$CH$_3$*)*, 1.41-1.32 (4 H, m, (2)-CHCH$_2$C*H$_2$*C*H$_2$*CH$_3$*)*, 0.94-0.91 (3 H, t, *J* 7.0, (2)-CHCH$_2$CH$_2$CH$_2$C*H$_3$*); δ_C (101 MHz, $CDCl_3$) 144.77 (*C*), 129.28 (*C*H), 126.72 (*C*H), 121.43 (*C*), 116.90 (*C*H), 114.05

(*C*H), 51.61 (*C*H), 36.46 (*C*H_2), 28.15 (*C*H_2), 27.96 (*C*H_2), 26.47 (*C*H_2), 22.88 (*C*H_2) and 14.10 (*C*H_3). The data matched that previously reported for this compound.

Reduction of **115l** using catalyst **175**; 92% ee and 64% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 14.0°C): t_R = 22.8 min (major), t_S = 25.6 (minor).

(*S*)-2-Phenyl-1,2,3,4-tetrahydroquinoline (115a').

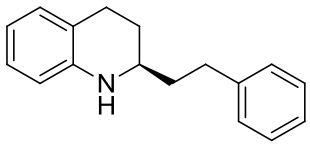


This is a known compound and has been fully characterised.[10h]

Reduction of **115** using catalyst **163b**; 73% ee and 68% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD, hexane:isopropanol = 90:10, flow rate 0.5 ml/min, 254 nm, 21.0°C): t_S = 17.0 min (major), t_R = 21.1 (minor); $[\alpha]_D^{27}$ -31.3 (*c* 0.5, $CHCl_3$) 73% ee (*S*) (lit.[10h] $[\alpha]_D^{25}$ +71.2 (*c* 1.0, $CHCl_3$) 72% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 7.40-7.26 (5 H, m, (2)-CHC$_6$*H*$_5$), 7.00 (2 H, m, (7)-C*H* + (5)-C*H*), 6.65 (1 H, t, *J* 6.7, (6)-C*H*), 6.55 (1 H, d, *J* 7.7, (8)-C*H*), 4.43 (1 H, dd, *J* 9.6, 3.3, (2)-C*H*), 4.04 (1 H, br s, (2)-N*H*), 2.97-2.88 (1 H, m, (4)-C*H*), 2.73 (1 H, dt, *J* 4.7, 16.4, (4)-C*H*), 2.15-2.09 (1 H, m, (3)-C*H*) and 2.04-1.94 (1 H, m, (3)-C*H*); δ_C (101 MHz, $CDCl_3$) 144.83 (*C*), 144.75 (*C*), 129.33 (*C*H), 128.60 (2 x *C*H), 127.47 (*C*H), 126.93 (*C*H), 126.58 (2 x *C*H), 120.90 (*C*), 117.18 (*C*H), 114.00 (*C*H), 56.28 (*C*H), 31.01 (*C*H_2) and 26.42 (*C*H_2). The data matched that previously reported for this compound.

Reduction of **115a** using catalyst **175**; 86% ee and 30% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.5 ml/min, 254 nm, 19.0°C): t_S = 17.1 min (major), t_R = 21.5 (minor).

(*R*)-2-Phenethyl-1,2,3,4-tetrahydroquinoline (117a').



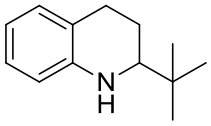
This is a known compound and has been fully characterised.[10h]

Reduction of **117a** using catalyst **163b**; 50% ee and 90% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD, hexane:isopropanol = 90:10, flow rate 0.5 ml/min, 254 nm, 20.0°C): t_R = 17.8 min (major), t_S = 19.5 (minor); $[\alpha]_D^{25}$ +45.5 (*c* 0.5, $CHCl_3$) 50% ee (*R*) (lit.[10h] $[\alpha]_D^{25}$ -73.1 (*c* 0.55, $CHCl_3$) 92% ee (*S*)); δ_H (300 MHz, $CDCl_3$) 7.30-7.16 (5 H, m, (2)-$CHCH_2CH_2C_6H_5$), 6.97-6.92 (2 H, m, (7)-C*H* + (5)-C*H*), 6.59 (1 H, td, *J* 7.5, 1.1, (6)-C*H*), 6.42 (1 H, dd, *J* 8.4, 1.3, (8)-C*H*), 3.80 (1 H, br s, (1)-N*H*), 3.31-3.22 (1 H, m, (2)-C*H*), 2.85-2.66 (4 H, m, (4)-CH_2 + (2)-$CHCH_2CH_2C_6H_5$), 2.01-1.92 (1 H, m, (3)-C*H*), 1.84-1.77 (2 H, m, (2)-$CHCH_2CH_2C_6H_5$) and 1.71-1.59 (1 H, m, (3)-C*H*); δ_C (75 MHz, $CDCl_3$) 143.90 (*C*), 141.30 (*C*), 128.66 (*C*H), 127.89 (2 x *C*H), 127.76 (2 x *C*H), 126.14 (*C*H), 125.37 (*C*H), 120.70 (*C*), 116.43 (*C*H), 113.53 (*C*H), 50.51 (*C*H), 37.70 (CH_2), 31.60 (CH_2), 27.40 (CH_2) and 25.60 (CH_2). The data matched that previously reported for this compound.

Reduction of **117a** using catalyst **175**; 93% ee and 57% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H,

hexane:isopropanol = 90:10, flow rate 0.5 ml/min, 254 nm, 15.0°C): t_R = 19.7 min (major), t_S = 21.7 (minor).

2-*tert*-Butyl-1,2,3,4-tetrahydroquinoline (178').

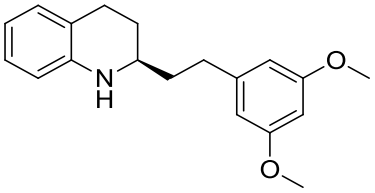


This is a known compound and has been fully characterised.[32j]

Reduction of **178** using catalyst **163b**; 0% ee and 57% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.5 ml/min, 254 nm, 15.0°C): t_R = 20.5 min, t_S = 27.5; δ_H (300 MHz, $CDCl_3$) 6.98-6.94 (2 H, m, (7)-C*H* + (5)-C*H*), 6.52 (1 H, td, *J* 7.5, 1.2, (6)-C*H*), 6.45 (1 H, d, *J* 7.7, (8)-C*H*), 3.78 (1 H, br s, (1)-N*H*), 3.00-2.96 (1 H, m, (2)-C*H*), 2.83-2.70 (2 H, m, (4)-CH_2), 2.00-1.95 (1 H, m, (3)-C*H*), 1.60-1.55 (1 H, m, (3)-C*H*), 0.98 (9 H, s, (2)-CHC(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 144.84 (*C*), 128.40 (*C*H), 126.10 (*C*H), 120.86 (*C*), 116.10 (*C*H), 113.40 (*C*H), 60.30 (*C*H), 32.79 (*C*), 26.84 (*C*H_2), 25.40 (3 x *C*H_3), 22.49 (*C*H_2). The data matched that previously reported for this compound.

Reduction of **178** using catalyst **175**; 0% ee and 16% conversion; HPLC (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 14.0°C): t_R = 20.6 min, t_S = 27.9.

(+)-2-(3,5-Dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline (195').



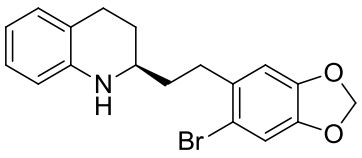
This compound is novel.

Reduction of **195** using catalyst **163b**; 67% ee and 93% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 80:20, flow rate 0.6 ml/min, 254 nm, 18.0°C): t_R = 28.1 min (major), t_S = 36.8 (minor); *$[\alpha]_D^{24}$ +39.5 (*c* 0.5, $CHCl_3$) 67% ee (*R*); υ_{max} 3675, 3396, 2935, 2838, 1594, 1460, 1428, 1351, 1309, 1276, 1254, 1203, 1148, 1114, 1056, 924, 830, 746, 718, 696 and 667 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.98-6.90 (2 H, m, (7)-C*H* + (5)-C*H*), 6.60 (1 H, td, *J* 7.5, 1.2, (6)-C*H*), 6.45 (1 H, dd, *J* 8.4, 1.4, (8)-C*H*), 6.38-6.35 (2 H, d, *J* 2.3, (2)-CH_2CH_2Ar(*o*-C*H*'s), 6.32-6.28 (1 H, t, *J* 2.3, (2)-CH_2CH_2Ar(*p*-C*H*), 3.77 (6 H, s, (2)-CH_2CH_2Ar(*m*-OCH_3's), 3.34-3.25 (1 H, m, (2)-C*H*), 2.81-2.72 (2 H, m, (4)-CH_2), 2.69-2.63 (2 H, m, (2)-CH_2CH_2Ar), 2.2-1.94 (1 H, m, (3)-C*H*), 1.85-1.75 (2 H, m, (2)-CH_2CH_2Ar) and 1.72-1.60 (1 H, m, (3)-C*H*); δ_C (75 MHz, $CDCl_3$) 160.88 (2 x *C*), 144.51 (*C*) 144.28 (*C*), 129.26 (*C*H), 126.75 (*C*H), 121.29 (*C*), 117.04 (*C*H), 114.15 (*C*H), 106.44 (2 x *C*H), 97.84 (*C*H), 55.29 (*C*H), 51.11 (2 x *C*H_3), 37.99 (*C*H_2), 32.49 (*C*H_2), 27.94 (*C*H_2) and 26.17 (*C*H_2); *m/z* (ESI-MS) 298.1 $[M+H]^+$. Found (ESI-HR-MS): 298.1798 $[M+H]^+$, $C_{19}H_{24}NO_2$ requires 298.1802 (1.3 ppm error).

Reduction of **195** using catalyst **175**; 94% ee and 58% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 80:20, flow rate 0.6 ml/min, 254 nm, 19.0°C): t_R = 27.4 min (major), t_S = 35.9 (minor).

*The absolute configuration has not been determined, but is assigned by analogy with the reduction product of substrate **117a**.

(+)-2-(2-(6-Bromobenzo[d][1,3]dioxol-5-yl)ethyl)-1,2,3,4-tetrahydroquinoline (194').



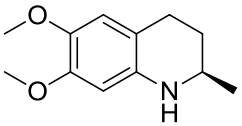
This compound is novel.

Reduction of **194** using catalyst **163b**; 47% ee and 86% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 80:20, flow rate 0.6 ml/min, 254 nm, 19.0°C): t_S = 21.2 min (major), t_R = 29.2 (minor); *$[\alpha]_D^{25}$ +25.6 (*c* 0.5, $CHCl_3$) 47% ee (*R*); υ_{max} 3664, 3410, 2912, 1606, 1585, 1500, 1473, 1434, 1408, 1353, 1309, 1275, 1227, 1111, 1066, 1035, 964, 931, 858, 832, 746, 718 and 657 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.98 (1 H, s, (2)-CH_2CH_2Ar(*m*-C*H*)), 6.96-6.92 (2 H, m, (5)-C*H* + (7)-C*H*), 6.70 (1 H, s, (2)-CH_2CH_2Ar(*o*-C*H*)), 6.59 (1 H, td, *J* 7.3, 1.2, (6)-C*H*), 6.45 (1 H, dd, *J* 8.7, 1.3, (8)-C*H*), 5.90 (2 H, s, (2)-$CH_2CH_2Ar(O_2CH_2)$), 3.84 (1 H, br s, (1)-N*H*), 3.38-3.30 (1 H, m, (2)-C*H*), 2.88-2.72 (4 H, m, (2)-CH_2CH_2Ar + (4)-CH_2), 2.10-2.00 (1 H, m, (3)-C*H*) and 1.88-1.60 (3 H, m, (2)-CH_2CH_2Ar + (3)-C*H*); δ_C (75 MHz, $CDCl_3$) 146.83 (*C*), 146.09 (*C*), 143.89 (*C*), 133.53 (2 x *C*), 128.64 (*C*H), 126.14 (*C*H), 120.66 (*C*), 116.46 (*C*H), 113.55 (*C*H), 112.12 (*C*H), 109.11 (*C*H), 100.99 (CH_2), 50.29 (*C*H), 36.37 (CH_2), 31.54 (CH_2), 27.22 (CH_2) and 25.60 (CH_2); *m/z* (ESI-MS) 360.1 $[M+H]^+$. Found (ESI-HR-MS): 360.0596 $[M+H]^+$, $C_{18}H_{19}BrNO_2$ requires 360.0594 (-0.7 ppm error).

Reduction of **194** using catalyst **175**; 81% ee and 30% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 80:20, flow rate 0.6 ml/min, 254 nm, 19.0°C): t_S = 21.1 min (major), t_R = 29.1 (minor).

*The absolute configuration has not been determined, but is assigned by analogy with the reduction product of substrate **117a**.

(+)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (193').



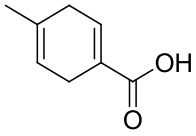
This compound is novel.

Reduction of **193** using catalyst **163b**; 48 % ee and 53 % conversion. Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 150 °C, P = 15 psi, H_2, imine 111.1 min., *S* isomer 113.6 min (minor)., *R* isomer 116.0 min (major)); $[\alpha]_D^{30}$ +64.0 (*c* 0.5, $CHCl_3$) 48 % ee (*R*); υ_{max} 3369, 2930, 2843, 1618, 1516, 1449, 1398, 1375, 1335, 1317, 1255, 1229, 1200, 1133, 1069, 1021, 1001, 962, 937, 909, 844 and 762 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.53 (1 H, s, (5)-C*H*), 6.11 (1 H, s, (8)-C*H*), 3.79 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 3.55-3.05 (1 H, br s, N*H*), 3.37-3.27 (1 H, m, (2)-C*H*), 2.84-2.73 (1 H, m, (4)-C*H*), 2.69-2.59 (1 H, m, (4)-C*H*), 1.96-1.86 (1 H, m, (3)-C*H*), 1.63-1.49 (1 H, m, (3)-C*H*) and 1.20 (3 H, d, *J* 6.3, CH_3); δ_C (101 MHz, $CDCl_3$) 148.17 (*C*), 141.37 (*C*), 138.68 (*C*), 113.68 (*C*H), 112.54 (*C*), 99.57 (*C*H), 56.71 (*C*H), 55.84 (*C*H_3), 47.40 (*C*H_3), 30.53 (*C*H_2), 26.16 (*C*H_2) and 22.52 (*C*H_3); *m/z* (ESI-MS) 208.1 $[M+H]^+$. Found (ESI-HR-MS): 208.1330 $[M+H]^+$, $C_{12}H_{18}NO_2$ requires 208.1332 (1.1 ppm error).

*The absolute configuration has not been determined, but is assigned by analogy with the reduction product of substrate **120a**.

4.2 Procedures from Section 2.2.

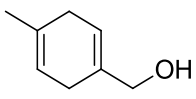
Synthesis of 4-methylcyclohexa-1,4-dienecarboxylic acid (199).



This compound has been reported but not fully characterised.[27a]

To a solution of propiolic acid (25.0 g, 22.0 cm^3, 357 mmol) in toluene was added, isoprene (25.28 g, 37.13 cm^3, 371.2 mmol) and hydroquinone (0.55 g, 5.01 mmol). The reaction was fitted with a condenser and heated to 130 °C overnight. The reaction mixture was cooled to room temperature, and a solid precipitate was filtered off and washed with cold toluene to give carboxylic acid **199** (26.5 g, 191.81 mmol, 54 %) as a white crystalline solid; Mp 181-184 °C; ν_{max} 3675, 2963, 2882, 2631, 2532, 1701, 1666, 1645, 1425, 1282, 1161, 1097, 1035, 1027, 957, 922, 800, 780, 736 and 716 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.10 (1 H, br s, C*H*=CCO_2H), 5.48 (1 H, br s, C*H*=CCH_3), 2.98-2.88 (2 H, m, CH_2C=CH), 2.82-2.72 (2 H, m, C=CCH_2) and 1.70 (3 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 172.44 (*C*OOH), 139.17 (*C*H), 129.23 (*C*), 127.07 (*C*), 118.55 (*C*H), 31.99 (CH_2), 25.48 (CH_2), 22.76 (CH_3); *m/z* (ESI-MS) 137.0 $[M-H]^+$. Found (ESI-HR-MS): 137.0620 $[M-H]^+$, $C_8H_9O_2$ requires 137.0608 (-8.6 ppm error). The data matched that previously reported for this compound.

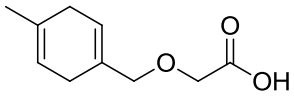
Synthesis of (4-methylcyclohexa-1,4-dien-1-yl)methanol (200).



This compound is novel.

4-Methylcyclohexa-1,4-dienecarboxylic acid (5.64 g, 40.8 mmol) in THF (50 cm^3) was added drop wise to a solution of $LiAlH_4$ (4.64 g, 123 mmol) in THF (250 cm^3) stirring at 0 °C. After addition, the solution was allowed to stir at rt over the weekend. The solution was then cooled to 0 °C and quenched with a 50 : 50 mixture of water and THF (50 cm^3: 50 cm^3), followed by water (50 cm^3). Rochelle salt (40 g, 142.12 mmol) was then added followed by DCM (75 cm^3) and was further allowed to stir for 3 hrs. As the Rochelle salt absorbs all the water, the remaining solution was then filtered off through celite, dried ($MgSO_4$), filtered and concentrated to give the alcohol as a white solid **200** (4.1 g, 33 mmol, 81 %); Mp 39-43 °C; ν_{max} 3361, 2963, 2908, 2818, 1429, 1338, 1185, 1140, 1065, 1001, 949, 904, 835 and 783 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.70 (1 H, s, C*H*=CCH_2OH), 5.45 (1 H, s, C*H*=CCH_3), 4.03 (2 H, s, CH_2OH), 2.72-2.65 (2 H, m, CH_2C=CH), 2.64-2.58 (2 H, m, C=CCH_2) and 1.68 (3 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 134.85 (*C*), 131.11 (*C*), 120.30 (*C*H), 118.25 (*C*H), 67.08 (*C*H_2), 31.26 (*C*H_2), 27.43 (*C*H_2) and 23.02 (*C*H_3); *m/z* (ESI-MS) 271.2 $[2M+Na]^+$. Found (ESI-HR-MS): 271.1673 $[2M+Na]^+$, $C_{16}H_{24}NaO_2$ requires 271.1669 (-1.6 ppm error).

Synthesis of 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)acetic acid (202).

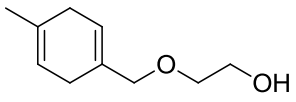


This compound is novel.

To a flame-dried flask containing (4-methylcyclohexa-1,4-dienyl)methanol **200** (3.73 g, 30.0 mmol), *tert*-butyl bromoacetate (6.92 g, 5.20 cm^3, 35.5 mmol) and TBAB (1.94 g, 6.01 mmol) was added NaOH solution (9.27 g in 9.27 cm^3 H_2O, 232 mmol) at 0 °C. The reaction mixture was then stirred at 70 °C for 3 days. Saturated NaCl solution (60 cm^3) was then added to the reaction mixture and then it was extracted using Et_2O (3 x 90

cm^3) to remove starting materials and other impurities. Conc. HCl was then added to the aqueous layer to obtain pH 1, and it was then extracted again using Et_2O (3 x 90 cm^3), dried ($MgSO_4$), filtered and concentrated to give the product **202** as an orange oil (4.1 g, 22.50 mmol, 75 %); ν_{max} 2963, 2855, 2819, 1724, 1426, 1244, 1196, 1106, 1055, 952, 903, 834, 786, 764, 734 and 668 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.99 (1 H, br s, COO*H*), 5.74 (1 H, s, C*H*=CCH_2O), 5.44 (1 H, s, C*H*=CCH_3), 4.08 (2 H, s, OCH_2COOH), 4.02 (2 H, s, CH=CCH_2O), 2.71-2.59 (4 H, m, $CH_2C(CH_3)$=CCH_2) and 1.67 (3 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 175.51 (*C*OOH), 130.95 (*C*), 130.74 (*C*), 124.22 (C*H*), 118.25 (C*H*), 75.53 (CH_2), 65.93 (CH_2), 31.33 (CH_2), 27.64 (CH_2) and 22.97 (CH_3); *m/z* (ESI-MS) 181.0 $[M-H]^+$. Found (ESI-HR-MS): 205.0840 $[M+Na]^+$, $C_{10}H_{14}NaO_3$ requires 205.0835 (-2.5 ppm error).

Synthesis of 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)ethanol (203).

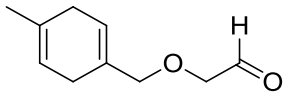


This compound is novel.

2-((-4-Methylcyclohexa-1,4-dienyl)methoxy)acetic acid **202** (4.10 g, 22.5 mmol) in THF (28 cm^3) was added dropwise to a solution of $LiAlH_4$ (2.56 g, 67.5 mmol) in THF (138 cm^3) with stirring at 0 °C. After addition, the solution was allowed to stir at rt for 72h. The solution was then cooled to 0 °C and quenched with a 50 : 50 mixture of water and THF (28 cm^3: 28 cm^3), followed by water (28 cm^3). Rochelle salt (40 g, 142.12 mmol) was then added followed by DCM (41 cm^3) and was further allowed to stir for 3 hrs. The remaining solution was then filtered off through celite, dried ($MgSO_4$), filtered and concentrated to give a light orange oil **203** (3.92 g, quantitative conversion, includes traces of solvent) which was characterised in crude form due to reoxidation during

chromatography; ν_{max} 3393, 2855, 2819, 1446, 1428, 1351, 1259, 1142, 1105, 1051, 951, 908, 889, 842, 783, 764 and 712 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.71 (1 H, s, C*H*=CCH_2O), 5.44 (1 H, s, C*H*=CCH_3), 3.93 (2 H, s, CH=CC*H*$_2$O), 3.73 (2 H, t, *J* 4.8, OC*H*$_2$$CH_2OH$), 3.50 (2 H, *J* 4.8, OCH_2C*H*$_2$OH), 2.70-2.58 (4 H, m, C*H*$_2$C(CH_3)=CC*H*$_2$), 2.17 (1 H, br s, O*H*) and 1.68 (3 H, s, C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 132.04 (*C*), 130.90 (*C*), 122.55 (*C*H), 118.34 (*C*H), 75.26 (*C*H_2), 70.75 (*C*H_2), 61.92 (*C*H_2), 31.31 (*C*H_2), 27.74 (*C*H_2) and 23.01 (*C*H_3); *m/z* (ESI-MS) 191.0 $[M+Na]^+$. Found (ESI-HR-MS): 191.1045 $[M+Na]^+$, $C_{10}H_{16}NaO_2$ requires 191.1043 (-1.1 ppm error).

Synthesis of 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)acetaldehyde (204).

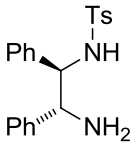


This compound is novel.

The solution of oxalylchloride (2M in DCM, 15.14 cm^3, 30.28 mmol) in anhydrous DCM (30 cm^3) was cooled to -78 °C, and was slowly added a solution of dimethylsulfoxide (4.73 g, 4.30 cm^3, 60.56 mmol) in DCM (15 cm^3) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 2-((4-methylcyclohexa-1, 4-dien-1-yl) methoxy) ethanol **203** (3.92 g, 23.3 mmol) in DCM (50 cm^3) was slowly added at the same temperature. After stirring for 40 min at -78 °C, Et_3N (14.22 g, 19.59 cm^3, 139.58 mmol) was added and the reaction mixture was allowed to warm up to rt. After 30 mins, water (100 cm^3) was added, and extracted with DCM, dried ($MgSO_4$), filtered and then concentrated under vacuum to give the product as a orangey brown oil **204** (4.78 g, quantitative conversion, includes traces of solvent) which was characterised in crude form due to reoxidation and decomposition during

attempts to purify; ν_{max} 2855, 2820, 1736, 1428, 1380, 1217, 1142, 1099, 952, 908, 752, 733 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.72 (1 H, s, C*H*O), 5.73 (1 H, s, C*H*=CCH_2O), 5.44 (1 H, s, C*H*=CCH_3), 4.03 (2 H, s, OC*H*$_2$CHO), 3.99 (2 H, s, CH=CC*H*$_2$O), 2.72-2.57 (4 H, m, C*H*$_2$C(CH_3)=CC*H*$_2$) and 1.68 (3 H, s, C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 200.98 (*C*HO), 131.16 (*C*), 130.84 (*C*), 124.03 (*C*H), 118.21 (*C*H), 75.82 (*C*H_2), 74.82 (*C*H_2), 31.33 (*C*H_2), 27.69 (*C*H_2) and 22.99 (*C*H_3); *m/z* (ESI-MS) 189.2 $[M+Na]^+$. Found (ESI-HR-MS): 189.0901 $[M+Na]^+$, $C_{10}H_{14}NaO_2$ requires 189.0886 (-7.6 ppm error).

Synthesis of *N*-((1*R*, 2*R*)-2-Amino-1, 2-diphenylethyl)-4-methylbenzenesulfonamide (81).

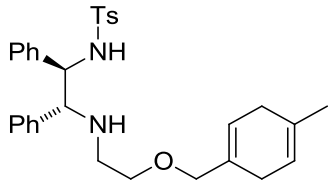


This is a known compound and has been fully characterised.[27c]

A solution of *p*-TsCl (4.5 g, 24.0 mmol) in THF (50 cm^3) was added to a mixture of (1*R*,2*R*)-(-)-1, 2-diphenylethylenediamine (5.0 g, 24.0 mmol) in THF (200 cm^3) and triethylamine (10 cm^3) over a period of 30 mins at 0 °C. After stirring for 12 hrs the solvent was removed under reduced pressure. The remaining solid was treated with aqueous sat. $NaHCO_3$ solution (400 cm^3) and DCM (400 cm^3). The organic phase was washed with brine, dried (Na_2SO_4), and then concentrated *in vacuo*. The crude product was purified by flash chromatography (100 % ethyl acetate) giving yellow white crystals **81** (7.1 g, 19.37 mmol, 81 %); δ_H (400 MHz, $CDCl_3$) 7.31 (2 H, d, *J* 8.3, $NHSO_2Ar$(*o*-2C*H*), 7.20-7.08 (10 H, m, 2C_6H_5), 6.98 (2 H, d, *J* 8.3, $NHSO_2Ar$(*m*-2C*H*), 6.00 (1 H, br s, N*H*Ts), 4.37 (1 H, d, *J* 5.1, TsNHC*H*), 4.13 (1 H, d, *J* 5.1, NH_2C*H*),

2.32 (3 H, s, $NHSO_2Ar(CH_3)$; δ_C (101 MHz, $CDCl_3$) 142.39 (*C*), 141.27 (*C*), 139.40 (*C*), 136.69 (*C*), 129.12 (*C*H), 128.43 (*C*H), 128.26 (*C*H), 127.39 (*C*H), 127.06 (*C*H), 126.99 (*C*H), 126.85 (*C*H), 126.50 (*C*H), 63.11 (*C*H), 60.52 (*C*H) and 21.42 (CH_3).

Synthesis of 4-methyl-*N*-((1*R*, 2*R*)-2-((2-((4-methylcyclohexa-1, 4-dien-1-yl)methoxy)ethyl)amino)-1, 2-diphenylethyl)benzenesulfonamide (205).

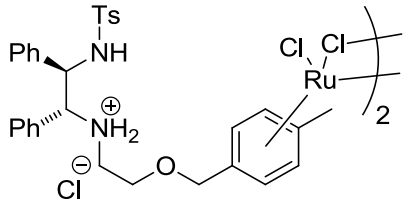


This compound is novel.

To a suspension of powdered molecular sieves (4 Å, 4.2 g) in dry methanol (250 cm^3) was added 2-((4-methylcyclohexa-1,4-dienyl)methoxy)acetaldehyde **204** (2.90 g, 17.43 mmol), (*R*,*R*)-TsDPEN **81** (7.10 g, 19.37 mmol) and glacial acetic acid (51 drops). The reaction mixture was stirred at rt and monitored by TLC. After 2 hrs, the imine had formed, and sodium cyanoborohydride (1.30 g, 21.05 mmol) was added. The reaction was left overnight at rt. The molecular sieves were removed by filtration, and the solution was concentrated under reduced pressure. The residue was re-dissolved in DCM (300 cm^3). The organic phase was washed with saturated $NaHCO_3$ (300 cm^3) and brine (300 cm^3), dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by flash chromatography (10→50 % v/v ethyl acetate/pet ether) to give **205** as a colourless oil (2.58 g, 5.00 mmol, 29 %); $[\alpha]_D^{26}$ -5.6 (*c* 0.5, $CHCl_3$); ν_{max} 3270, 3029, 2855, 1599, 1495, 1454, 1397, 1327, 1218, 1184, 1156, 1092, 1027, 931, 812, 752, 699 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36 (2 H, d, *J* 8.2, $NHSO_2Ar$(*o*-2C*H*)), 7.15-6.90 (12 H, m, $2C_6H_5$ + $NHSO_2Ar$(*m*-2C*H*)), 6.30 (1 H, br s, N*H*Ts), 5.62 (1 H, s C*H*=CCH_2O), 5.45 (1 H, s, C*H*=CCH_3), 4.24 (1 H, d, *J* 7.6, TsNHC*H*), 3.77 (2 H, s,

CH=CC*H*$_2$O), 3.66 (1 H, d, *J* 7.6, NHC*H*), 3.45-3.32 (2 H, m, NHCH$_2$*CH*$_2$OCH$_2$), 2.65-2.54 (5 H, m, NHC*H*$_{(1)}$H$_{(2)}$*C*H$_2$OCH$_2$ + C*H*$_2$C(CH$_3$)=CC*H*$_2$), 2.48-2.41 (1 H, m, NHCH$_{(1)}$*H*$_{(2)}$*C*H$_2$OCH$_2$), 2.33 (3 H, s, NHSO$_2$ArC*H*$_3$), 1.73 (1 H, br s, N*H*CH) and 1.69 (3 H, s, CH$_2$C(C*H*$_3$)=CCH$_2$); δ_C (101 MHz, CDCl$_3$) 142.62 (*C*), 139.21 (*C*), 138.42 (*C*), 137.12 (*C*), 132.17 (*C*), 130.92 (*C*), 129.08 (*C*H), 128.30 (*C*H), 127.92 (*C*H), 127.77 (*C*H), 127.55 (*C*H), 127.46 (*C*H), 127.26 (*C*H), 127.12 (*C*H), 122.00 (*C*H), 118.42 (*C*H), 75.00 (*C*H$_2$), 69.00 (*C*H$_2$), 67.83 (*C*H$_3$), 63.10 (*C*H$_3$), 46.74 (*C*H$_2$), 31.33 (*C*H$_2$) and 27.74 (*C*H$_2$); *m/z* (ESI-MS) 539.2 $[M+Na]^+$. Found (ESI-HR-MS): 517.2519 $[M+H]^+$, $C_{31}H_{37}N_2O_3S$ requires 517.2519 (0.1 ppm error).

Synthesis of ether linked "tethered" dimer (206).

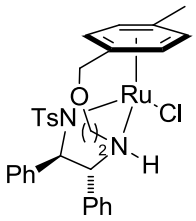


This compound is novel.

To a stirred solution of 4-methyl-*N*-((1*R*,2*R*)-2-(2-((4-methylcyclohexa-1,4-dienyl)methoxy)ethylamino)-1,2-diphenylethyl)benzenesulfonamide **205** (1.38 g, 2.67 mmol) in DCM (39 cm^3) was added 1.25 M HCl in EtOH (6.4 cm^3, 8.01 mmol). The reaction mixture was stirred for 2 hrs and concentrated under vacuum. To a suspension of the residue in IPA (28 cm^3) was added trihydrated ruthenium trichloride (880 mg, 4.22 mmol). The reaction mixture was stirred at reflux temperature for 2 days. It was then filtered off and washed with cold IPA to give a dark blue solid **206** (1.70 g, 1.18 mmol, 88 %); ν_{max} 3676, 2988, 2902, 1454, 1406, 1394, 1382, 1324, 1250, 1230, 1155, 1066, 1057, 892, 812, 763, 699 and 669 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$) 9.47 (2 H, br s, 2 x N*H*$_{(1)}$H$_{(2)}^+$Cl$^-$), 8.90 (2 H, br s, 2 x NH$_{(1)}$*H*$_{(2)}^+$Cl$^-$), 8.55 (2 H, d, *J* 9.8, 2 x N*H*Ts),

7.35-6.70 (28 H, m, 2 x (14 x Ar-*H*)), 6.05-5.75 (8 H, m, 2 x (4 x Ru-Ar-*H*)), 4.80 (2 H, t, *J* 9.8, 2 x C*H*$NH_2^+Cl^-$), 4.63-4.50 (2 H, m, 2 x C*H*NHTs), 4.38 (3.2 H, s, 2 x ArCH_2O), 4.31 (0.8 H, s, 2 x ArCH_2O), 3.90-3.75 (4 H, m, 2 x $NH_2^+Cl^-CH_2CH_2$O), 3.10-2.97 (4 H, m, 2 x $NH_2^+Cl^-CH_2CH_2$O), 2.21 (6 H, s, 2 x CH_3Ts), 2.15 (4.8 H, s, 2 x CH_3Ar) and 2.12 (1.2 H, s, 2 x CH_3Ar); δ_C (101 MHz, DMSO-d_6) 142.66 (2 x *C*), 138.06 (2 x *C*), 135.90 (2 x *C*), 131.93 (2 x *C*), 129.52 (2 x (2 x *C*H)), 129.50 (2 x *C*H and 2 x (2 x *C*H)), 129.21 (2 x (2 x *C*H)), 128.55 (2 x *C*H), 128.28 (2 x (2 x *C*H)), 128.15 (2 x (2 x *C*H)), 126.88 (2 x (2 x *C*H)), 122.62 (2 x *C*H), 118.73 (2 x *C*H), 102.76 (2 x *C*), 94.90 (2 x *C*), 65.59 (2 x *C*H), 62.48 (2 x (2 x *C*H)), 60.85 (2 x *C*H), 56.78 (2 x (2 x CH_2)), 48.61 (2 x CH_2), 26.00 (2 x CH_3) and 21.53 (2 x CH_3); *m/z* (ESI-MS) 615.0 $[Monomer+H]^+$. Found (ESI-HR-MS): 615.1266 $[Monomer+H]^+$, $C_{31}H_{33}N_2O_3{}^{102}RuS$ (monomer formed *in situ* from dimer and loss of 3 x HCl) requires 615.1257 (-2.0 ppm error). **Optical rotation could not be obtained due to the product being highly coloured.**

Synthesis of ether linked "tethered" monomer (207).



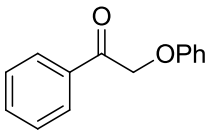
This compound is novel.

To a suspension of dimer **206** (98 mg, 0.07 mmol) in IPA (9 cm^3) was added Et_3N (0.06 cm^3, 0.42 mmol). After stirring at 80 °C for 1.5 hrs, the hot IPA solution was filtered through a layer of cotton wool and filter paper to remove impurities. The solution was then concentrated, re-dissolved in DCM and washed with water. The organic layer was

then dried (Na_2SO_4), filtered and concentrated to give the monomer **207** as an orange solid (29 mg, 0.0446 mmol, 33 %)**.** The crude product was isolated, and ^{1}H NMR, LRMS and HRMS were carried out to confirm the presence of product. Several purification attempts on the crude product led to decomposition of the material; δ_H (300 MHz, $CDCl_3$) 7.30 (2 H, d, *J* 8.0, 2 x Ar-*H*), 7.15-7.10 (4 H, m, 4 x Ar-*H*), 6.85 (2 H, d, *J* 8.0, 2 x Ar-*H*), 6.80-6.70 (2 H, m, 2 x Ar-*H*), 6.70-6.55 (4 H, m, 4 x Ar-*H*), 6.15-6.05 (1 H, m, Ru-Ar-*H*), 5.75 (1H, d, *J* 6.4, Ru-Ar-H), 5.65 (1H, d, *J* 6.4, RuArH), 5.50-5.40 (1 H, m RuArH), 4.92 (1 H, brd, *J* 14.2, CHPh), 4.55-4.45 (2 H, m, CHPh + NH), 4.05-3.88 (4 H, m, 2 x CH_2), 3.65-3.55 (1 H, m, C*H*H), 3.20-3.05 (1 H, m, CH*H*), 2.60 (3 H, s, CH_3), 2.24 (3 H, s, CH_3); *m/z* (ESI-MS) 615.0 $[Monomer+H]^+$. Found (ESI-HR-MS): 615.1264 $[Monomer+H]^+$, $C_{31}H_{33}N_2O_3{}^{102}RuS$ requires 615.1257 (-1.8 ppm error).

The ^{1}H NMR spectroscopic data of the monomeric complex obtained by Ikariya matched that of the crude material obtained from dimer **206** in this project.[27i]

Synthesis of 2-phenoxy-1-phenylethanone (222).

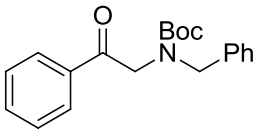


This is a known compound and has been fully characterised.[32k]

Phenol (2.05 g, 1.91 cm^3, 21.80 mmol) and potassium carbonate (2.70 g, 19.50 mmol) were dissolved in acetone (40 cm^3) and the mixture was stirred for about 10 minutes. Phenacyl bromide (3.53 g, 17.70 mmol) was added to the mixture and the mixture was refluxed for 2 hrs. The reaction mixture was then quenched with water (100 cm^3) and the phenacyl ether was extracted with diethyl ether (3 x 50 cm^3). The organic extracts were washed with 2M NaOH (3 x 50 cm^3), and water (3 x 50 cm^3), dried ($MgSO_4$) and

filtered. The solvent was concentrated under reduced pressure and a white solid was obtained. The crude was recrystallized with ethanol to give **222** as a white crystalline sold (1.73 g, 8.15 mmol, 46 %); δ_H (400 MHz, $CDCl_3$) 8.01 (2 H, d, *J* 7.1, 2 x Ar-*H o* to C(C=O)CH_2OPh), 7.62 (1 H, t, *J* 7.1, Ar-*H p* to C(C=O)CH_2OPh), 7.50 (2 H, t, *J* 7.1, 2 x Ar-*H m* to C(C=O)CH_2OPh) 7.33-7.25 (2 H, m, 2 x Ar-*H m* to OCH_2COPh), 7.02-6.92 (3 H, m, 2 x Ar-*H o* and 1 x Ar-*H p* to OCH_2COPh) and 5.27 (2 H, s, CH_2); δ_C (101 MHz, $CDCl_3$) 194.58 (*C*=O), 158.04 (*C*), 134.64 (*C*), 133.88 (*C*H), 129.60 (2 x *C*H), 128.85 (2 x *C*H), 128.18 (2 x *C*H), 121.68 (*C*H), 114.84 (2 x *C*H) and 70.84 (CH_2); *m/z* (ESI-MS) 235.1 $[M+Na]^+$. The data matched that previously reported for this compound.

Synthesis of *tert*-butyl benzyl(2-oxo-2-phenylethyl)carbamate (225).

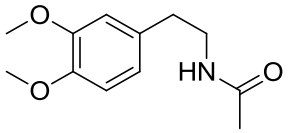


This is a known compound and has been fully characterised.[32l]

Benzylamine (1.02 g, 9.5 mmol) and triethylamine (5.06 g, 50.0 mmol) were stirred in dichloromethane (20 cm^3) for 30 minutes. 2-Bromoacetophenone (1.99 g, 10.00 mmol) in dichloromethane (10 cm^3) was added dropwise and the reaction was stirred for 3 hrs. Di-*tert*-butyl dicarbonate (2.18 g, 10.0 mmol) in dichloromethane (10 cm^3) was added and the reaction mixture was stirred overnight. Saturated ammonium chloride solution (30 cm^3) was added,the phases were separated and the aqueous layer extracted with dichloromethane (3 x 20 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*, to give the crude as a yellow oil. Purification by flash chromatography (5→10% v/v ethyl acetate/pet ether) gave **225** as a light yellow solid (1.80 g, 5.53 mmol, 58 %); δ_H (300 MHz, $CDCl_3$) (1 : 1 mixture of NCO

rotamers) 7.93-7.21 (10 H, m, 10 x Aryl-*H*), 4.63 (1 H, s, C(=O)-C*H*$_{(1)}$H$_{(2)}$), 4.61 (1 H, s, C(=O)-CH$_{(1)}$*H*$_{(2)}$), 4.56 (1 H, s, C*H*$_{(1)}$H$_{(2)}$-Ph), 4.46 (1 H, s, CH$_{(1)}$*H*$_{(2)}$-Ph), 1.50 (4.5 H, s, C*H*$_3$) and 1.41 (4.5 H, s, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 195.87 (*C*=O), 155.27 (*C*=O), 137.24 (*C*), 134.65 (*C*), 132.85 (*C*H), 128.13 (*C*H), 127.98 (3 x *C*H), 127.53 (*C*H), 127.29 (*C*H), 127.07 (*C*H), 126.92 (*C*H), 126.86 (*C*H), 80.01 ((CH$_3$)$_3$*C*), 51.51 (N(Boc)*C*H$_2$), 50.76 (C(=O)*C*H$_2$) and 27.79 ((*C*H$_3$)$_3$C). The data matched that previously reported for this compound.

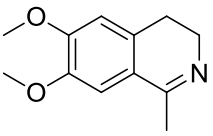
Synthesis of *N*-(3,4-Dimethoxyphenethyl)acetamide (306).



This is a known compound and has been fully characterised.[27h]

2-(3,4-Dimethoxyphenyl)ethylamine (5.00 g, 4.70 cm^3, 27.60 mmol) was dissolved in dichloromethane (50 cm^3) and stirred. Acetic anhydride (2.80 g, 2.60 cm^3, 27.60 mmol) was then added dropwise, and the solution was left to stir for 1 hr. After the stirring was completed, the solution was washed with saturated citric acid (10 cm^3), saturated $NaHCO_3$ (10 cm^3), brine (10 cm^3) and then dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure giving **306** as a white solid (5.50 g, 24.63 mmol, 90 %); δ_H (300 MHz, $CDCl_3$) 6.84-6.79 (1 H, m, Ar-*H*), 6.77-6.70 (2 H, m, 2 x Ar-*H*), 5.60 (1 H, br s, N*H*), 3.88 (3 H, s, OC*H*$_3$), 3.87 (3 H, s, OC*H*$_3$), 3.49 (2 H, d, *J* 7.0, NHC*H*$_2$), 2.77 (2 H, *J* 7.0, Ar-C*H*$_2$) and 1.95 (3 H, s, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.40 (*C*), 149.27 (*C*), 147.92 (*C*), 131.58 (*C*), 120.86 (*C*H), 112.08 (*C*H), 111.56 (*C*H), 56.17 (*C*H$_3$), 56.13 (*C*H$_3$), 41.04 (*C*H$_2$), 35.44 (*C*H$_2$) and 23.61 (*C*H$_3$). The data matched that previously reported for this compound.

Synthesis of 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (109a).

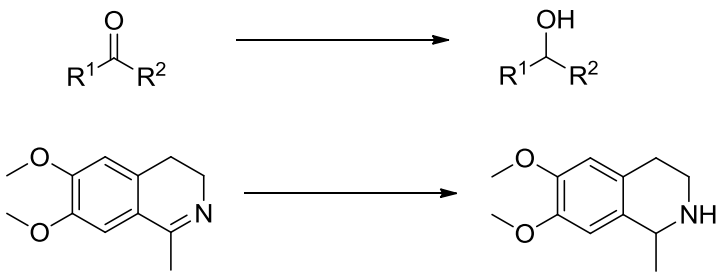


This is a known compound and has been fully characterised.[27h]

N-(3-4-Dimethoxyphenethyl)acetamide **306** (5.50 g, 24.67 mmol) and $POCl_3$ (3.78 g, 2.26 cm^3, 24.7 mmol) were refluxed in toluene (50 cm^3) for 2 hrs. Once the reflux was completed, the solvent was removed *in vacuo* and the residue was re-dissolved in dichloromethane (50 cm^3). The organic layer was washed with saturated K_2CO_3 (2 x 20 cm^3), brine (20 cm^3) and was then dried (Na_2SO_4). After filtration the solvent was removed *in vacuo* giving **109a** (4.44 g, 21.63 mmol, 88 %) as a yellow solid; δ_H (300 MHz, $CDCl_3$) 7.00 (1 H, s, Ar-*H*), 6.70 (1 H, s, Ar-*H*), 3.91 (6 H, s, 2 x OC*H*$_3$), 3.62 (2 H, t, *J* 7.4, NC*H*$_2$), 2.63 (2 H, t, *J* 7.4, Ar-C*H*$_2$) and 2.37 (3 H, s, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 164.20 (*C*), 150.70 (*C*), 147.30 (*C*), 130.96 (*C*), 122.30 (*C*), 110.11 (*C*H), 108.86 (*C*H), 56.07 (*C*H_3), 55.82 (*C*H_3), 46.83 (*C*H_2), 25.61 (*C*H_2) and 23.28 (*C*H_3). The data matched that previously reported for this compound.

Ketone and Imine Reduction.

General procedure for the preparation of secondary alcohols and amines.



Method A (Racemic) To a stirred solution of ketone/imine (1 mmol) in methanol (12 cm^3) was added $NaBH_4$ (3.0 eq.) portion-wise and the reaction mixture was allowed to stir until completion while monitoring the conversion by TLC, after completion the solution was diluted with saturated $NH_4Cl_{(aq)}$ (12 cm^3) and extracted with dichloromethane (3 x 12 cm^3). The combined extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the racemic secondary alcohol or amine.

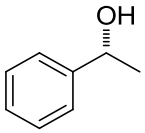
Method B (Asymmetric) using "tethered" Ru (II) dimer for ketones A solution of ruthenium dimer (0.0025 mmol) in formic acid/triethylamine (5:2) azeotrope (0.5 cm^3) was stirred in a flame dried Schlenk tube (The Schlenk tube was degassed and purged with argon 3x before and after the addition of reagents) at 28 °C for 30 minutes. Ketone (1 mmol) was added and dichloromethane (0.5 cm^3) was added if required to dissolve the substrate. The reaction mixture was stirred at 28 °C and monitored by TLC or GC, for which a drop of sample was filtered through a small plug of silica in a glass pipette using ethyl acetate and maybe a few drops of methanol depending on the polarity of the compound. After completion, the reaction mixture was diluted with dichloromethane (6.7 cm^3) and washed with $NaCO_3$ solution (3 x 5 cm^3). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the desired alcohol.

Method C (Asymmetric) using "tethered" Ru (II) dimer for imines A solution of ruthenium dimer (0.0025 mmol) and imine (1 mmol) in methanol (1.6 cm^3) was stirred in a flame dried Schlenk tube at 28 °C for 10 minutes. Formic acid/triethylamine (5:2) azeotrope (0.5 cm^3) was then added (The Schlenk tube was degassed and purged with argon 3x before and after the addition of reagents). The reaction mixture was stirred at 28 °C and monitored by TLC or GC, for which a drop of sample was filtered through a small plug of silica in a glass pipette using ethyl acetate and maybe a few drops of methanol depending on the polarity of the compound. After completion, $NaHCO_3$

solution (5 cm^3) was added, and was extracted with dichloromethane (3 x 6.7 cm^3). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the desired amine.

Reduction product analysis.

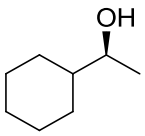
(*R*)-1-Phenylethanol (49a').



This is a known compound and has been fully characterised.[20a]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β- 236M-19 50m, T = 115 °C, P = 15 psi, H_2, *R* isomer 15.0 min., *S* isomer 16.7 min.); $[\alpha]_D^{28}$ +56.0 (*c* 1.0, $CHCl_3$) >99% ee (*R*) (lit.[20a] $[\alpha]_D^{22}$ +49.0 (*c* 1.0, $CHCl_3$) 98% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 7.39-7.24 (5 H, m, 5 x Ar-*H*), 4.88 (1 H, q, *J* 6.4, C*H*OH), 2.03 (1 H, br s, O*H*) and 1.49 (3 H, d, *J* 6.4, CH_3); δ_C (101 MHz, $CDCl_3$) 145.83 (*C*), 128.52 (2 x *C*H), 127.49 (*C*H), 125.41 (2 x *C*H), 70.43 (*C*H) and 25.16 (CH_3). The data matched that previously reported for this compound.

(*S*)-1-Cyclohexylethanol (141').

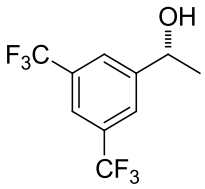


This is a known compound and has been fully characterised.[32m]

Using catalyst **183**; Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, (Product was converted to (*S*)-1-cyclohexylethyl acetate

for GC separation) T = 115 °C, P = 15 psi, He, *S* isomer 24.6 min., *R* isomer 27.6 min.); $[\alpha]_D^{28}$ +5.6 (*c* 1.0, $CHCl_3$) 74% ee (*S*) (lit.[32m] $[\alpha]_D^{22}$ +2.7 (*c* 0.5, $CHCl_3$) 75% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 3.58-3.51 (1 H, m, C*H*OH), 1.90-1.62 (5 H, m, cyclohexyl), 1.50 (1 H, br s, O*H*), 1.32-0.91 (6 H, m, cyclohexyl) and 1.16 (3 H, d, *J* 6.3, CH_3); δ_C (101 MHz, $CDCl_3$) 72.22 (*C*H), 45.13 (*C*H), 28.71 (*C*H_2), 28.37 (*C*H_2), 26.53 (*C*H_2), 26.24 (*C*H_2), 26.15 (*C*H_2) and 20.37 (*C*H_3). The data matched that previously reported for this compound.

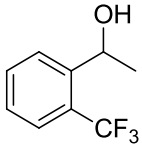
(*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)ethanol (129').



This is a known compound and has been fully characterised.[32n]

Enantiomeric excess and conversion by GC analysis (CP-Chirasil-Dex CB, 25 m, 0.25 mm, 0.25 µm, T = 100 °C for 10 minutes then ramp at 10 °C/minute to 200 °C, P = 20 psi, He, *S* isomer 11.0 min., *R* isomer 12.0 min.); $[\alpha]^{546}_{28}$ +11.2 (*c* 1.0, $CHCl_3$) 60% ee (*R*) (lit.[32n] $[\alpha]^{546}_{22}$ +16.0 (*c* 1.2, $CHCl_3$) >99% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 7.85 (2 H, s, 2 x Ar-*H o* to CHOH), 7.79 (1 H, s, Ar-*H p* to CHOH), 5.05 (1 H, q, *J* 6.5, C*H*OH), 2.02 (1 H, br s, O*H*) and 1.55 (3 H, d, *J* 6.5, CH_3); δ_C (101 MHz, $CDCl_3$) 148.22 (*C*), 131.92 (*C*), 131.59 (*C*), 125.66 (2 x *C*H), 124.71 (*C*), 121.94 (*C*), 121.31 (*C*H), 69.28 (*C*H) and 25.60 (*C*H_3). The data matched that previously reported for this compound.

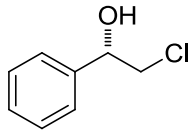
1-(2-(Trifluoromethyl)phenyl)ethanol (224').



This is a known compound and has been fully characterised.[17l]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 110 ^{o}C, P = 15 psi, H_2, *R* isomer 18.3 min., *S* isomer 20.0 min.); (lit.[17l] $[\alpha]_D^{29}$ -30.4 (*c* 1.41, $CHCl_3$) 96% ee (*R*)); δ_H (300 MHz, $CDCl_3$) 7.82 (1 H, d, *J* 7.8 , Ar-*H o* to CF_3), 7.63-7.55 (2 H, m, Ar-*H o* to $CHOHCH_3$ and Ar-*H p* to $CHOHCH_3$), 7.40-7.32 (1 H, m, Ar-*H m* to $CHOHCH_3$ and *p* to CF_3), 5.37-5.27 (1 H, m, C*H*OH), 2.10 (1 H, d, *J* 3.0, O*H*) and 1.48 (3 H, d, *J* 6.3, CH_3); δ_C (75 MHz, $CDCl_3$) 144.41 (*C*), 131.77 (*C*H), 126.72 (*C*H), 126.47 (*C*H), 125.57 (*C*), 124.71 (*C*H), 121.94 (*C*), 65.06 (*C*H) and 24.79 (*C*H_3). The data matched that previously reported for this compound.

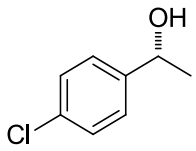
(*S*)-2-Chloro-1-phenylethanol (219').



This is a known compound and has been fully characterised.[20a]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β- 236M-19 50m, T = 140 °C, P = 10 psi, H_2, *S* isomer 29.9 min., *R* isomer 31.7 min.); $[\alpha]_D^{28}$ +43.4 (*c* 1.0, cyclohexane) >98% ee (*S*) (lit.[20a] $[\alpha]_D^{25}$ +51.5 (*c* 1.1, cyclohexane) 95% ee (*S*)); δ_H (300 MHz, $CDCl_3$) 7.33-7.15 (5 H, m, 5 x Ar-*H*), 4.76 (1 H, dd, *J* 8.7, 3.4, C*H*OH), 3.61 (1 H, dd, *J* 3.4, 11.2 C$H_{(1)}H_{(2)}$Cl), 3.51 (1 H, dd, *J* 8.7, 11.2, $CH_{(1)}H_{(2)}$Cl) and 2.60 (1 H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 139.27 (*C*), 128.07 (2 x *C*H), 127.87 (*C*H), 125.44 (2 x *C*H), 73.46 (*C*H) and 50.31 (*C*H_2). The data matched that previously reported for this compound.

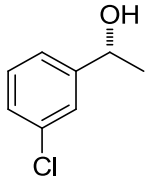
(*R*)-1-(4-Chlorophenyl)ethanol (49c').



This is a known compound and has been fully characterised.[32o]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β- 236M-19 50m, T = 130 °C, P = 15 psi, H_2, *R* isomer 27.9 min., *S* isomer 31.4 min.); $[\alpha]_D^{20}$ +50.4 (*c* 1.0, $CHCl_3$) 96% ee (*R*) (lit.[32o] $[\alpha]_D^{22}$ +45.6 (*c* 1.0, $CHCl_3$) 91% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 7.33-7.25 (4 H, m, 4 x Ar-*H*), 4.87 (1 H, q, *J* 6.5, C*H*OH), 2.73 (1 H, br s, O*H*) and 1.47 (3 H, d, *J* 6.5, C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 144.17 (*C*), 133.12 (*C*), 128.80 (2 x *C*H), 126.82 (2 x *C*H), 69.81 (*C*H) and 25.24 (*C*H_3). The data matched that previously reported for this compound.

(*R*)-1-(3-Chlorophenyl)ethanol (49b').

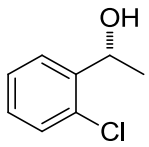


This is a known compound and has been fully characterised.[33a]

Enantiomeric excess and conversion by GC analysis (CP-Chirasil-Dex CB, 25 m, 0.25 mm, 0.25 µm, T = 120 °C for 20 minutes then ramp at 15 °C/minute to 200 °C, P = 20 psi, He, *R* isomer 19.2 min., *S* isomer 21.1 min.); $[\alpha]_D^{29}$ +34.8 (*c* 1.0, $CHCl_3$) 94% ee (*R*) (lit.[33a] $[\alpha]_D^{22}$ +43.3 (*c* 1.0, $CHCl_3$) 90% ee (*R*)); δ_H (300 MHz, $CDCl_3$) 7.37-7.32 (1 H, m, Ar-*H o* to Cl and $CHOHCH_3$), 7.30-7.19 (3 H, m, 1 x Ar-*H m* to Cl/$CHOHCH_3$ and 1 x Ar-*H p* to Cl and 1 x Ar-*H p* to $CHOHCH_3$), 4.85 (1 H, q, *J* 6.5, C*H*OH), 2.50 (1 H, br s, O*H*) and 1.46 (3 H, d, *J* 6.5, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 147.18 (*C*), 133.74

(*C*), 129.18 (*C*H), 126.92 (*C*H), 125.02 (*C*H), 122.93 (*C*H), 69.29 (*C*H) and 24.59 (CH_3). The data matched that previously reported for this compound.

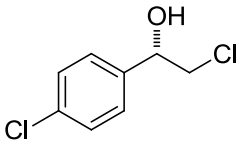
(*R*)-1-(2-Chlorophenyl)ethanol (216').



This is a known compound and has been fully characterised.[32o]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β- 236M-19 50m, T = 130 °C, P = 15 psi, H_2, *R* isomer 22.9 min., *S* isomer 28.8 min.); $[\alpha]_D^{29}$ +49.2 (*c* 1.0, $CHCl_3$) 87% ee (*R*) (lit.[32o] $[\alpha]_D^{22}$ +40.8 (*c* 1.0, $CHCl_3$) 77% ee (*R*)); δ_H (300 MHz, $CDCl_3$) 7.59 (1 H, dd, *J* 1.8, 1.8, Ar-*H o* to Cl), 7.34-7.25 (2 H, m, 1 x Ar-*H o* to $CHOHCH_3$ and 1 x Ar-*H p* to $CHOHCH_3$), 7.19 (1 H, ddd, *J* 1.8, 1.8, 1.8, Ar-*H p* to Cl), 5.29 (1 H, q, *J* 6.4, C*H*OH), 2.20 (1 H, br s, O*H*) and 1.49 (3 H, d, *J* 6.4, CH_3); δ_C (75 MHz, $CDCl_3$) 142.41 (*C*), 131.02 (*C*), 128.79 (*C*H), 127.79 (*C*H), 126.60 (*C*H), 125.79 (*C*H), 66.36 (*C*H) and 22.88 (CH_3). The data matched that previously reported for this compound.

(*S*)-2-Chloro-1-(4-chlorophenyl)ethanol (220').

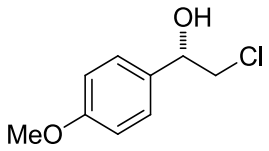


This is a known compound and has been fully characterised.[20a]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β- 236M-19 50m, T = 160 °C, P = 11 psi, H_2, *S* isomer 38.2 min., *R* isomer 40.9 min.); $[\alpha]_D^{31}$

+44.8 (*c* 1.0, $CHCl_3$) 96% ee (*S*) (lit.[20a] $[\alpha]_D^{25}$ +47.0 (*c* 1.1, $CHCl_3$) 93% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 7.37-7.30 (4 H, m, 4 x Ar-*H*), 4.88 (1 H, dd, *J* 3.5, 8.6, C*H*OH), 3.71 (1 H, dd, *J* 3.5, 11.3, $CH_{(1)}H_{(2)}Cl$), 3.61 (1 H, dd, *J* 8.6, 11.3, $CH_{(1)}H_{(2)}Cl$) and 2.95 (1 H, br s, O*H*); δ_C (101 MHz, $CDCl_3$) 138.37 (*C*), 134.26 (*C*), 128.86 (2 x *C*H), 127.47 (2 x *C*H), 73.39 (*C*H) and 50.67 (CH_2). The data matched that previously reported for this compound.

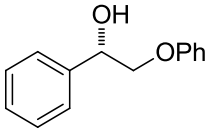
(*S*)-2-Chloro-1-(4-methoxyphenyl)ethanol (221').



This is a known compound and has been fully characterised.[20a]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β- 236M-19 50m, T = 160 °C, P = 14 psi, H_2, *S* isomer 33.2 min., *R* isomer 34.6 min.); $[\alpha]_D^{31}$ +50.0 (*c* 1.0, $CHCl_3$) 97% ee (*S*) (lit.[20a] $[\alpha]_D^{24}$ +52.9 (*c* 1.1, $CHCl_3$) 95% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 7.34-7.27 (2 H, m, 2 x Ar-*H o* to $CHOHCH_2Cl$), 6.93-6.87 (2 H, m, 2 x Ar-*H o* to MeO), 4.85 (1 H, dd, *J* 3.6, 8.7, C*H*OH), 3.81 (3 H, s, CH_3O), 3.70 (1 H, dd, *J* 3.6, 11.2, $CH_{(1)}H_{(2)}Cl$), 3.63 (1 H, dd, *J* 8.7, 11.2, $CH_{(1)}H_{(2)}Cl$) and 2.65 (1 H, br s, O*H*); δ_C (101 MHz, $CDCl_3$) 159.72 (*C*-OMe), 132.06 (*C*), 127.35 (2 x *C*H), 114.09 (2 x *C*H), 73.75 (*C*H), 55.33 (CH_3) and 50.92 (CH_2). The data matched that previously reported for this compound.

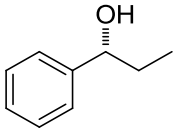
(*S*)-2-Phenoxy-1-phenylethanol (222').



This is a known compound and has been fully characterised.[33b]

Enantiomeric excess by HPLC analysis and conversion by GC analysis (ChiralPak IA Column: 0.46 cm^3 x 25 cm, hexane:isopropanol = 95:5, flow rate 0.5 ml/min, 254 nm, 24 °C: t_R = 28.9 min (minor), t_S = 36.4 (major)); $[\alpha]_D^{30}$ +58.8 (*c* 1.0, $CHCl_3$) 95% ee (*S*) (lit.[33b] $[\alpha]_D^{20}$ +50.0 (*c* 1.7, $CHCl_3$) 98% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 7.47-7.23 (7 H, m, 5 x Ar-*H* and 2 x Ar-*H m* to CH_2O), 6.97 (1 H, t, *J* 7.4, Ar-*H p* to CH_2O), 6.91 (2 H, d, *J* 7.8, 2 x Ar-*H o* to CH_2O), 5.12 (1 H, dd, *J* 3.2, 8.8, C*H*OH), 4.10 (1 H, dd, *J* 3.2, 9.6, $CH_{(1)}H_{(2)}$OPh), 4.01 (1 H, t, *J* 9.6, 8.8, $CH_{(1)}H_{(2)}$OPh) and 2.90 (1 H, br s, O*H*); δ_C (101 MHz, $CDCl_3$) 158.41 (*C*), 139.66 (*C*), 129.60 (2 x *C*H), 128.61 (2 x *C*H), 128.23 (*C*H), 126.32 (2 x *C*H), 121.35 (*C*H), 114.68 (2 x *C*H), 73.32 (CH_2) and 72.63 (*C*H). The data matched that previously reported for this compound.

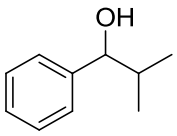
(*R*)-1-phenylpropan-1-ol (49g').



This is a known compound and has been fully characterised.[32b]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 110 °C, P = 15 psi, H_2, *R* isomer 31.1 min., *S* isomer 33.8 min.); $[\alpha]_D^{26}$ +53.6 (*c* 1.0, $CHCl_3$) >99% ee (*R*) (lit.[32b] $[\alpha]_D^{26}$ -40.0 (*c* 0.85, $CHCl_3$) 66% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 7.38-7.24 (5 H, m, 5 x Ar-*H*), 4.59 (1 H, t, *J* 6.5, C*H*OH), 2.40 (1 H, br s, O*H*), 1.90-1.68 (2 H, m, CH_2) and 0.91 (3 H, t, *J* 7.4, CH_3); δ_C (101 MHz, $CDCl_3$) 144.55 (*C*), 128.43 (2 x *C*H), 127.54 (*C*H), 125.99 (2 x *C*H), 76.09 (*C*H), 31.88 (CH_2) and 10.15 (CH_3). The data matched that previously reported for this compound.

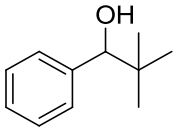
2-Methyl-1-phenylpropan-1-ol (217').



This is a known compound and has been fully characterised.[33c]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 110 °C, P = 15 psi, H_2, *R* isomer 39.4 min., *S* isomer 40.8 min.); (lit.[33c] $[\alpha]_D^{20}$ +34.6 (*c* 1.0, $CHCl_3$) 68.5% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 7.36-7.22 (5 H, m, 5 x Ar-*H*), 4.33 (1 H, d, *J* 6.8, C*H*OH), 1.97 (1 H, br s, O*H*), 1.94 (1 H, oct, *J* 6.8, C*H*$(CH_3)_2$), 0.99 (3 H, d, *J* 6.8, CH_3) and 0.78 (3 H, d, *J* 6.8, CH_3); δ_C (101 MHz, $CDCl_3$) 143.68 (*C*), 127.94 (2 x *C*H), 127.01 (*C*H), 126.60 (2 x *C*H), 80.05 (*C*H), 35.09 (*C*H), 19.02 (*C*H_3) and 18.28 (*C*H_3). The data matched that previously reported for this compound.

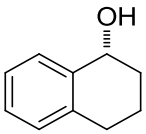
2,2-Dimethyl-1-phenylpropan-1-ol (218').



This is a known compound and has been fully characterised.[33d]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 125 ^oC, P = 15 psi, H_2, *S* isomer 29.5 min., *R* isomer 30.5 min.); (lit.[33d] $[\alpha]_D^{20}$ +12.2 (*c* 1.0, $CHCl_3$) 45% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 7.34-7.22 (5 H, m, 5 x Ar-*H*), 4.38 (1 H, s, C*H*OH), 1.92 (1 H, br s, O*H*) and 0.92 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 142.23 (*C*), 127.64 (2 x *C*H), 127.57 (2 x *C*H), 127.29 (*C*H), 82.41 (*C*H), 35.64 (*C*) and 25.96 (3 x *C*H_3). The data matched that previously reported for this compound.

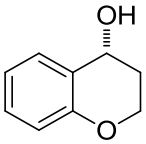
(*R*)-1,2,3,4-Tetrahydronaphthalen-1-ol (214').



This is a known compound and has been fully characterised.[33e]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 115 ^{o}C, P = 15 psi, H_2, *S* isomer 74.1 min., *R* isomer 74.3 min.); $[\alpha]_D^{29}$ -19.2 (*c* 1.0, $CHCl_3$) >99% ee (*R*) (lit.[33e] $[\alpha]_D^{20}$ +38.9 (*c* 1.45, $CHCl_3$) 99% ee (*S*)); δ_H (300 MHz, $CDCl_3$) 7.45-7.36 (1 H, m, 1 x Ar-*H*), 7.22-7.04 (3 H, m, 3 x Ar-*H*), 4.77 (1 H, t, *J* 4.4, C*H*OH), 2.88-2.62 (2 H, m, CH_2 *p* to CHOH), 2.50 (1 H, br s, O*H*) and 2.05-1.69 (4 H, m, 2 x CH_2 *o* and *m* to CHOH); δ_C (75 MHz, $CDCl_3$) 138.10 (*C*), 136.52 (*C*), 128.42 (*C*H), 128.06 (*C*H), 127.00 (*C*H), 125.58 (*C*H), 67.57 (*C*H), 31.62 (*C*H_2), 28.63 (*C*H_2) and 18.16 (*C*H_2). The data matched that previously reported for this compound.

(*R*)-Chroman-4-ol (215').

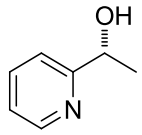


This is a known compound and has been fully characterised.[33e]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 160 ^{o}C, P = 15 psi, H_2, *S* isomer 13.4 min., *R* isomer 13.6 min.); $[\alpha]_D^{30}$ +77.6 (*c* 1.0, $CHCl_3$) >99% ee (*R*) (lit.[33e] $[\alpha]_D^{20}$ -62.0 (*c* 1.8, $CHCl_3$) 98% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 7.32 (1 H, dd, *J* 7.6, 1.6, Ar-*H*), 7.21 (1 H, dt, *J* 7.4, 1.6, Ar-*H*), 6.93 (1 H, dt, *J* 7.4, 1.1, Ar-*H*), 6.85 (1 H, d, *J* 8.3, Ar-*H*), 4.80 (1 H, t, *J* 4.0, C*H*OH), 4.31-4.24 (2 H, m, CH_2 *m* to CHOH), 2.18-2.09 (1 H, m, C$H_{(1)}H_{(2)}$ *o* to CHOH), 2.08-2.00 (1

H, m, $CH_{(1)}H_{(2)}$ *o* to CHOH) and 1.80 (1 H, br s, O*H*); δ_C (101 MHz, $CDCl_3$) 154.45 (*C*), 129.76 (*C*H), 129.64 (*C*H), 124.42 (*C*), 120.62 (*C*H), 117.11 (*C*H), 63.29 (*C*H), 61.93 (CH_2) and 30.84 (CH_2). The data matched that previously reported for this compound.

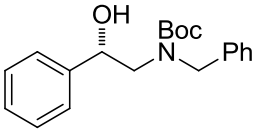
(*R*)-1-(Pyridin-2-yl)ethanol (107a').



This is a known compound and has been fully characterised.[20a]

Using catalyst **163b**; Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, (Product was converted to (*R*)-1-(pyridin-2-yl)ethyl acetate for GC separation) T = 115 ^oC, P = 15 psi, G = H_2, *S* isomer 19.3 min., *S* isomer 20.0 min.); $[\alpha]_D^{28}$ +24.8 (*c* 1.0, $CHCl_3$) 88% ee (*R*) (lit.[20a] $[\alpha]_D^{24}$ +18.9 (*c* 1.5, $CHCl_3$) 91% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 8.55 (1 H, d, *J* 4.9, Ar-*H o* to N), 7.76 (1 H, dt, *J* 7.8, 1.7, Ar-*H p* to N), 7.38 (1 H, d, *J* 7.8, Ar-*H o* to $CHOHCH_3$), 7.29-7.24 (1 H, m, Ar-*H m* to N and *p* to $CHOHCH_3$), 4.95 (1 H, q, *J* 6.6, C*H*OH) and 1.53 (3 H, d, *J* 6.6, CH_3); δ_C (101 MHz, $CDCl_3$) 163.01 (*C*), 147.48 (*C*H), 137.77 (*C*H), 122.61 (*C*H), 120.31 (*C*H), 68.97 (*C*H) and 23.95 (CH_3). The data matched that previously reported for this compound.

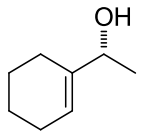
(*S*)-*tert*-Butyl benzyl(2-hydroxy-2-phenylethyl)carbamate (225').



This is a known compound and has been fully characterised.[32l]

Enantiomeric excess by HPLC analysis and conversion by NMR analysis (ChiralPak IA Column: 0.46 cm^3 x 25 cm, hexane:isopropanol = 98:2, flow rate 0.5 ml/min, 254 nm, 21 °C: t_R = 49.6 min (minor), t_S = 64.9 (major)); $[\alpha]_D^{29}$ +2.4 (*c* 0.5, ethanol) >99% ee (*S*) (lit.[32l] $[\alpha]_D^{20}$ +3.3 (*c* 2.0, ethanol) 80% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 7.34-7.15 (10 H, m, 10 x Ar-*H*), 4.92-4.86 (1 H, m, C*H*OH), 4.51-4.41 (2 H, m, $CH_{(1)}H_{(2)}$-Ar and O*H*), 4.19 (1 H, d, *J* 14.4, $CH_{(1)}H_{(2)}$-Ar), 3.64-3.49 (1 H, m, CH(OH)$CH_{(1)}H_{(2)}$), 3.33 (1 H, d, *J* 13.0, CH(OH)$CH_{(1)}H_{(2)}$) and 1.49 (9 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 155.91 (*C*=O) 142.39 (*C*), 137.96 (*C*), 128.62 (4 x *C*H), 128.41 (*C*H), 127.51 (*C*H), 127.38 (*C*H), 127.34 (*C*H), 125.80 (2 x *C*H), 81.51 ($(CH_3)_3C$), 74.23 (*C*H(OH)), 57.30 (CH_2), 52.53 (CH_2) and 28.42 ($(CH_3)_3C$); *m/z* (ESI-MS) 350.2 $[M+Na]^+$. The data matched that previously reported for this compound.

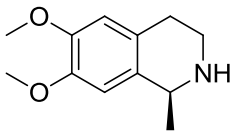
(*R*)-1-(Cyclohex-1-en-1-yl)ethanol (226').



This is a known compound and has been fully characterised.[33f]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 115 °C, P = 15 psi, H_2, *S* isomer 13.5 min., *R* isomer 13.9 min.); $[\alpha]_D^{30}$ +26.4 (*c* 0.5, $CHCl_3$) 71% ee (*R*) (lit.[33f] $[\alpha]_{589}^{20}$ +19.7 (*c* 1.69, $CHCl_3$) 83% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 5.66 (1 H, s, C*H*=C), 4.16 (1 H, q, *J* 6.4, C*H*OH), 2.10-1.90 (4 H, m, 2 x CH_2), 1.72-1.49 (5 H, m, 2 x CH_2 + OH) and 1.25 (3 H, d, *J* 6.4, CH_3); δ_C (101 MHz, $CDCl_3$) 141.27 (*C*), 121.49 (*C*H), 72.14 (*C*H), 24.89 (CH_2), 23.67 (CH_2), 22.66 (CH_2), 22.60 (CH_2) and 21.50 (CH_3). The data matched that previously reported for this compound.

(*S*)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (109a').

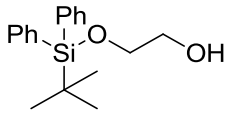


This is a known compound and has been fully characterised.[26a]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 170 ^{o}C, P = 15 psi, He, *S* isomer 35.5 min., *R* isomer 36.1 min.); $[\alpha]_D^{27}$ -40.0 (*c* 0.5, $CHCl_3$) 87% ee (*R*) (lit.[26a] $[\alpha]_D^{28}$ -32.9 (*c* 0.3, $CHCl_3$) 84% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 6.63 (1 H, s, Ar-*H*), 6.57 (1 H, s, Ar-*H*), 4.05 (1 H, q, *J* 6.6, C*H*NH), 3.85 (6 H, s, 2 x CH_3O), 3.29-3.21 (1 H, m, C$H_{(1)}$H$_{(2)}$ *p* to CH(CH_3)), 3.04-2.95 (1 H, m, CH$_{(1)}H_{(2)}$ *p* to CH(CH_3)), 2.85-2.73 (1 H, m, C$H_{(1)}$H$_{(2)}$ *m* to CH(CH_3)), 2.69-2.60 (1 H, m, CH$_{(1)}H_{(2)}$ *m* to CH(CH_3)), 1.73 (1 H, br s, N*H*) and 1.44 (3 H, d, *J* 6.6, CH_3); δ_C (101 MHz, $CDCl_3$) 147.30 (*C*), 147.22 (*C*), 132.52 (*C*), 126.85 (*C*), 111.77 (*C*H), 109.04 (*C*H), 56.00 (1 x *C*H_3O), 55.86 (1 x *C*H_3O), 51.25 (*C*H), 41.89 (*C*H_2), 29.61 (*C*H_2) and 22.90 (*C*H_3). The data matched that previously reported for this compound.

4.3 Procedures from Section 2.3.

Synthesis of 2-((*tert*-butyldiphenylsilyl)oxy)ethanol (230a).

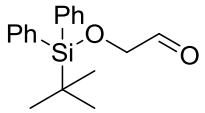


This is a known compound and has been fully characterised.[26c]

tert-Butyl-chlorodiphenylsilane (2.29 g, 2.17 cm^3, 8.33 mmol) was added to a stirred solution of ethane-1,2-diol (3.10 g, 2.79 cm^3, 50.00 mmol) and imidazole (0.63 g, 9.18 mmol) in THF (43 cm^3) under argon atmosphere. The resulting mixture was stirred for

24 hrs at rt and quenched with water (43 cm^3) followed by the addition of Et_2O (43 cm^3). After phase separation and extraction of the aqueous phase with Et_2O (3 x 43 cm^3), the combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography (10→20 % v/v ethyl acetate/pentane) to afford the monosilyl alcohol **230a** as a colourless oil (1.1 g, 3.66 mmol, 44 %); δ_H (400 MHz, $CDCl_3$) 7.74-7.64 (4 H, m, 4 x Ar-*H*), 7.48-7.35 (6 H, m, 6 x Ar-*H*), 3.80-3.74 (2 H, m, SiOC*H*$_2$), 3.72-3.65 (2 H, m, C*H*$_2$OH), 2.16 (1 H, t, *J* 6.2, O*H*) and 1.07 (9 H, s, 3 x C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 135.57 (4 x *C*H), 133.32 (2 x *C*), 129.84 (2 x *C*H), 127.81 (4 x *C*H), 65.03 (*C*H_2), 63.75 (*C*H_2), 26.88 (3 x *C*H_3) and 19.26 ($(CH_3)_3C$). The data matched that previously reported for this compound.

Synthesis of 2-((*tert*-butyldiphenylsilyl)oxy)acetaldehyde (231a).

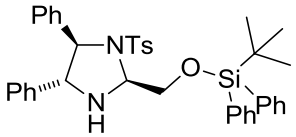


This is a known compound and has been fully characterised.[26c]

A solution of oxalylchloride (2M in DCM, 2.4 cm^3, 4.75 mmol) in anhydrous DCM (5 cm^3) was cooled to -78 °C, and was slowly added to a solution of dimethylsulfoxide (0.74 g, 0.68 cm^3, 9.52 mmol) in DCM (2.5 cm^3) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 2-((*tert*-butyldiphenylsilyl)oxy)ethanol **230a** (1.10 g, 3.66 mmol) in DCM (8 cm^3) was slowly added at the same temperature. After stirring for 40 min at -78 °C, Et_3N (2.24 g, 3.1 cm^3, 21.94 mmol) was added and the reaction mixture was allowed to warm up to rt. After 30 mins, water (16 cm^3) was added, and extracted with DCM, dried ($MgSO_4$), filtered and then concentrated under vacuum to give the product as a orange oil **231a** (1.09 g, 3.66 mmol, >99 % quantitative conversion, includes traces of solvent); δ_H (400 MHz, $CDCl_3$) 9.72 (1 H, s, C*H*O), 7.68-

7.64 (4 H, m, 4 x Ar-*H*), 7.48-7.37 (6 H, m, 6 x Ar-*H*), 4.22 (2 H, s, CH_2) and 1.10 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 201.73 (*C*H=O), 135.52 (4 x *C*H), 132.49 (2 x *C*), 130.08 (2 x *C*H), 127.94 (4 x *C*H), 70.00 (*C*H_2), 26.71 (3 x *C*H_3) and 19.27 ((CH_3)$_3$*C*). The data matched that previously reported for this compound.

Synthesis of (2*S*,4*R*,5*R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-4,5-diphenyl-1-tosylimidazolidine (232a).

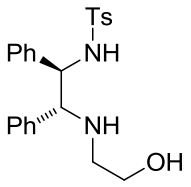


This is a known compound and has been fully characterised.[29a]

To a stirred solution of (*R*, *R*)-TsDPEN **81** (1.11 g, 3.04 mmol) and molecular sieves (4 Å, 2.1 g) in dry methanol (24 cm^3) was added a solution of 2-((*tert*-butyldiphenylsilyl)oxy)acetaldehyde **231a** (1.09 g, 3.66 mmol) in methanol (10 cm^3) followed by the addition of glacial acetic acid (0.21 cm^3). The reaction was stirred for 4 hrs during which time a white precipitate formed. The precipitate (molecular sieves and the product) was filtered off and washed with cold methanol. The remaining solid was washed thoroughly with DCM to separate the product from molecular sieves, and was then concentrated *in vacuo*. **232a** was obtained as a white solid (690 mg, 1.07 mmol, 35 %); δ_H (400 MHz, $CDCl_3$) 7.72 (4 H, td, *J* 8.2, 1.3, 4 x Ar-*H*), 7.51 (2 H, d, *J* 8.2, 2 x Ar-*H*), 7.48-7.34 (6 H, m, 6 x Ar-*H*), 7.29-7.12 (10 H, m, 10 x Ar-*H*), 6.90 (2 H, d, *J* 7.0, 2 x Ar-*H*), 4.91 (1 H, dd, *J* 6.1, 3.2, TsNC*H*NH), 4.48 (1 H, d, *J* 6.1, C*H*NTs), 4.17 (1 H, d, *J* 6.1, C$H_{(1)}H_{(2)}$OSi), 4.15 (1 H, d, *J* 6.1, C*H*NH), 4.07 (1 H, dd, *J* 10.7, 3.2, C$H_{(1)}H_{(2)}$OSi), 2.81 (1 H, br s, N*H*), 2.40 (3 H, s, CH_3Ts) and 1.09 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 143.63 (*C*), 139.81 (*C*), 138.76 (*C*), 135.74 (2 x *C*H), 135.70 (2 x

*C*H), 134.00 (*C*), 133.08 (*C*), 133.04 (*C*), 129.87 (2 x *C*H), 129.52 (2 x *C*H), 128.46 (2 x *C*H), 128.33 (2 x *C*H), 127.86 (4 x *C*H), 127.82 (2 x *C*H), 127.57 (*C*H), 127.48 (*C*H), 126.89 (2 x *C*H), 126.75 (2 x *C*H), 77.30 (*C*H), 71.06 (*C*H), 69.07 (*C*H), 65.03 (CH_2), 26.97 (3 x CH_3), 21.56 (CH_3) and 19.29 (*C*). The data matched that previously reported for this compound.

Synthesis of *N*-((1*R*,2*R*)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (233).

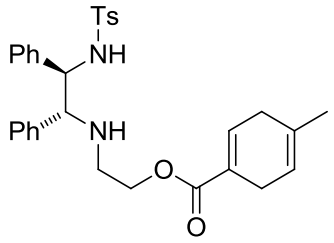


This is a known compound and has been fully characterised. [29a]

(2*S*,4*R*,5*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4,5-diphenyl-1-tosylimidazolidine **232a** (3.24 g, 5 mmol) in THF (7 cm^3) was added dropwise to a solution of $LiAlH_4$ (0.60 g, 15 mmol) in THF (31 cm^3) stirring at 0 °C. After addition, the solution was allowed to stir at rt over the weekend. The solution was then cooled to 0 °C and quenched with a 50 : 50 mixture of water and THF (6 cm^3: 6 cm^3), followed by water (6 cm^3). Rochelle salt (4.91 g, 17.40 mmol) was then added followed by DCM (9 cm^3) and was further allowed to stir for 3 hrs. The remaining solution was then filtered off through celite, dried ($MgSO_4$), filtered and concentrated to give the alcohol as a white solid **233** (1.58 g, 3.85 mmol, 77 %); δ_H (400 MHz, $CDCl_3$) 7.39 (2 H, d, *J* 8.2, 2 x Ar-*H*), 7.16-7.10 (3 H, m, 3 x Ar-*H*), 7.06-6.92 (7 H, m, 7 x Ar-*H*), 6.88-6.84 (2 H, m, 2 x Ar-*H*), 4.36 (1 H, d, *J* 8.2, C*H*Ts), 3.73 (1 H, d, *J* 8.2, C*H*NH), 3.71-3.63 (1 H, m, $CH_{(1)}H_{(2)}OH$), 3.63-3.55 (1 H, m, $CH_{(1)}H_{(2)}OH$), 2.62-2.47 (2 H, m, CH_2NH) and 2.32 (3 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 142.83 (*C*), 139.00 (*C*), 137.96 (*C*), 137.05 (*C*),

129.12 (2 x *C*H), 128.35 (2 x *C*H), 127.91 (2 x *C*H), 127.63 (2 x *C*H), 127.58 (*C*H), 127.55 (2 x *C*H), 127.26 (*C*H), 127.10 (2 x *C*H), 67.80 (*C*H), 63.32 (*C*H), 61.74 (CH_2), 49.03 (CH_2) and 21.45 (CH_3). The data matched that previously reported for this compound.

Synthesis of 2-(((1*R*,2*R*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)amino)ethyl 4-methylcyclohexa-1,4-dienecarboxylate (240).

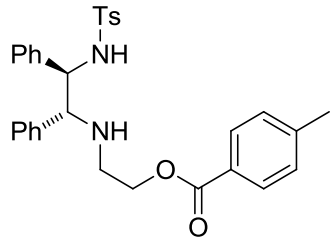


This compound is novel.

4-Methylcyclohexa-1,4-diene carboxylic acid (18 mg, 0.13 mmol) was added to a solution of *N*-((1*R*,2*R*)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **233** (53 mg, 0.13 mmol) in DCM (2 cm^3) at rt, followed by addition of DCC (165 mg, 0.80 mmol) and DMAP (16 mg, 0.13 mmol). The resulting mixture was stirred overnight and the concentrated under reduced pressure. The crude white residue was then purified by flash chromatography (10→30 % v/v ethyl acetate/hexane) giving **240** as a colourless gum (58 mg, 0.11 mmol, 84 %); $[\alpha]_D^{22}$ -10.4 (*c* 0.5, $CHCl_3$); ν_{max} 3663, 3259, 2902, 1712, 1690, 1651, 1600, 1495, 1454, 1395, 1327, 1304, 1252, 1185, 1157, 1092, 1048, 960, 920, 812, 756, 719, 699 and 668 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38 (2 H, d, *J* 8.3, 2 x Ar-*H*), 7.16-7.10 (3 H, m, 3 x Ar-*H*), 7.09-7.03 (3 H, m, 3 x Ar-*H*), 7.02-6.94 (6 H, m, 6 x Ar-*H*), 6.90-6.85 (1 H, m, C*H*=C(CO_2)), 6.04 (1 H, d, *J* 3.3, N*H*Ts), 5.50-5.45 (1 H, m, C*H*=C(CH_3)), 4.30 (1 H, dd, *J* 7.3, 3.3, C*H*NHTs), 4.25-4.17 (1 H, m, $CH_{(1)}H_{(2)}$OC=O), 4.09-4.02 (1 H, m, $CH_{(1)}H_{(2)}$OC=O),

3.74 (1 H, d, *J* 7.3, C*H*NH), 2.87-2.75 (4 H, m, CH_2C=CCH_2), 2.75-2.67 (1 H, m, C$H_{(1)}$H$_{(2)}$NH), 2.62-2.53 (1 H, m, CH$_{(1)}H_{(2)}$NH), 2.32 (3 H, s, CH_3Ts) and 1.72 (3 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 166.85 (*C*=O), 142.67 (*C*), 138.78 (2 x *C*), 138.36 (2 x *C*), 137.03 (*C*H), 129.39 (*C*), 129.10 (2 x *C*H), 128.42 (2 x *C*H), 128.04 (2 x *C*H), 127.64 (*C*H), 127.44 (2 x *C*H), 127.35 (3 x *C*H), 127.03 (2 x *C*H), 118.55 (*C*H), 67.14 (*C*H), 63.13 (*C*H_2), 63.07 (*C*H), 45.66 (*C*H_2), 31.89 (*C*H_2), 26.07 (*C*H_2), 22.83 (*C*H_3) and 21.42 (*C*H_3); *m/z* (ESI-MS) 531.1 $[M+H]^+$, 553.1 $[M+Na]^+$. Found (ESI-HR-MS): 531.2330 $[M+H]^+$, $C_{31}H_{35}N_2O_4S$ requires 531.2312 (-3.2 ppm error).

Synthesis of 2-(((1*R*,2*R*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)amino)ethyl 4-methylbenzoate (241).

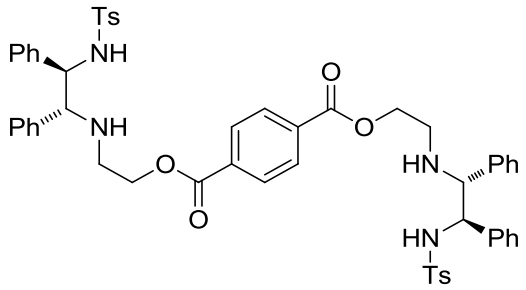


This compound is novel.

p-Toluic acid (18 mg, 0.13 mmol) was added to a solution of *N*-((1*R*, 2*R*)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **233** (53 mg, 0.13 mmol) in DCM (2 cm^3) at rt, followed by addition of DCC (165 mg, 0.80 mmol) and DMAP (16 mg, 0.13 mmol). The resulting mixture was stirred overnight and then concentrated under reduced pressure. The crude white residue was then purified by flash chromatography (10→30 % v/v ethyl acetate/hexane) giving **241** as white crystals (58 mg, 0.11 mmol, 84 %); Mp 61-64 °C; $[\alpha]_D^{23}$ -17.6 (*c* 0.5, $CHCl_3$); ν_{max} 3266, 3031, 1712, 1611, 1495, 1453, 1406, 1327, 1271, 1178, 1156, 1093, 1020, 917, 841, 812, 753, 698 and 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.83 (2 H, d, *J* 8.1, 2 x Ar-*H*), 7.33 (2 H, d, *J*

8.1, 2 x Ar-*H*), 7.25 (2 H, d, *J* 7.7, 2 x Ar-*H*), 7.18-7.09 (3 H, m, 3 x Ar-*H*), 7.08-7.01 (3 H, m, 3 x Ar-*H*), 6.98 (6 H, d, *J* 7.7, 6 x Ar-*H*), 6.07 (1 H, br s, N*H*Ts), 4.40-4.28 (1 H, m, C$H_{(1)}$H$_{(2)}$OC=O), 4.31 (1 H, d, *J* 7.3, C*H*NHTs), 4.26-4.17 (1 H, m, CH$_{(1)}$$H_{(2)}$OC=O), 3.77 (1 H, d, *J* 7.3, C*H*NH), 2.84-2.75 (1 H, m, C$H_{(1)}$H$_{(2)}$NH), 2.71-2.62 (1 H, m, CH$_{(1)}$$H_{(2)}$NH), 2.44 (3 H, s, C$H_3$Ts), 2.30 (3 H, s, C$H_3$) and 1.76 (1 H, br s, N*H*); δ_C (101 MHz, $CDCl_3$) 166.53 (*C*=O), 143.79 (*C*), 142.68 (*C*), 138.80 (*C*), 138.37 (*C*), 137.01 (*C*), 129.69 (2 x *C*H), 129.15 (2 x *C*H), 129.11 (2 x *C*H), 128.43 (2 x *C*H), 128.06 (2 x *C*H), 127.66 (*C*H), 127.46 (2 x *C*H), 127.35 (3 x *C*H), 127.20 (*C*), 127.04 (2 x *C*H), 67.29 (*C*H), 63.72 (*C*H$_2$), 63.11 (*C*H), 45.73 (*C*H$_2$), 21.72 (*C*H$_3$) and 21.41 (*C*H$_3$); *m/z* (ESI-MS) 529.1 $[M+H]^+$, 551.2 $[M+Na]^+$. Found (ESI-HR-MS): 529.2159 $[M+H]^+$, $C_{31}H_{33}N_2O_4S$ requires 529.2156 (-0.6 ppm error).

Synthesis of bis(2-(((1*R*,2*R*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)amino)ethyl) terephthalate (242).

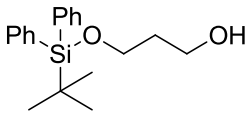


This compound is novel.

Terephthalic acid (11 mg, 0.065 mmol) was added to a solution of *N*-((1*R*, 2*R*)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **233** (53 mg, 0.13 mmol) in DCM (2 cm^3) at rt, followed by addition of EDC (150 mg, 0.80 mmol) and DMAP (16 mg, 0.13 mmol). The resulting mixture was stirred overnight and then water (2 cm^3) was added. The organic phase was separated from the aqueous, and then

DCM (2 x 2 cm^3) was further added to extract the remaining product from the aqueous layer. The organic layers were then combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure giving the crude product, which was then purified by flash chromatography (10→30 % v/v ethyl acetate/hexane) giving **242** as white crystals (14.5 mg, 0.02 mmol, 24 %); Mp 80-83 °C; $[\alpha]_D^{22}$ -54.4 (*c* 0.25, $CHCl_3$); ν_{max} 3272, 1716, 1599, 1495, 1454, 1408, 1325, 1267, 1155, 1092, 1018, 918, 876, 812, 767, 731, 698 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.10 (4 H, s, 4 x CO_2Ar-*H*), 7.36 (4 H, d, *J* 8.2, 4 x Ar-*H*), 7.21-7.06 (6 H, m, 6 x Ar-*H*), 7.05-6.91 (14 H, m, 14 x Ar-*H*), 6.91-6.84 (4 H, m, 4 x Ar-*H*), 6.20 (2 H, br s, 2 x N*H*Ts), 4.51-4.28 (2 H, m, 2 x C$H_{(1)}$$H_{(2)}$OC=O), 4.35-4.21 (4 H, m, 2 x C$H_{(1)}$$H_{(2)}$OC=O + C*H*NHTs), 3.81 (2 H, d, *J* 7.9, 2 x C*H*NH), 2.86-2.76 (2 H, m, 2 x C$H_{(1)}$$H_{(2)}$NH), 2.76-2.66 (2 H, m, 2 x C$H_{(1)}$$H_{(2)}$NH) and 2.29 (6 H, s, 2 x CH_3Ts); δ_C (101 MHz, $CDCl_3$) 165.61 (2 x *C*), 142.83 (2 x *C*), 138.76 (2 x *C*), 138.26 (2 x *C*), 136.96 (2 x *C*), 133.90 (2 x *C*), 129.77 (4 x *C*H), 129.14 (5 x *C*H), 128.38 (4 x *C*H), 128.01 (4 x *C*H), 127.63 (5 x *C*H), 127.30 (6 x *C*H), 127.09 (4 x *C*H), 67.44 (2 x *C*H), 64.24 (2 x *C*H_2), 63.52 (2 x *C*H), 45.74 (2 x *C*H_2) and 21.42 (2 x *C*H_3); *m/z* (ESI-MS) 951.1 $[M+H]^+$, 973.1 $[M+Na]^+$. Found (ESI-HR-MS): 476.1755 $[M+2H]^{2+}$, $C_{54}H_{56}N_4O_8S_2$ requires 476.1764 (2.6 ppm error).

Synthesis of 3-((*tert*-butyldiphenylsilyl)oxy)propan-1-ol (230b).

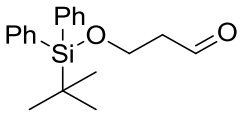


This is a known compound and has been fully characterised.[33g]

To a solution of 1,3-propanediol (0.85 g, 0.80 cm^3, 11.1 mmol) and imidazole (1.0 g, 14.45 mmol) in dry DCM (35 cm^3) was added *tert*-butyl-chlorodiphenylsilane (6.1 g, 5.8 cm^3, 22.2 mmol) dropwise under a nitrogen atmosphere at rt followed by stirring at

the same temperature for 4 hrs. The reaction mixture was then concentrated under reduced pressure and the residue was then purified by flash chromatography (1→9 % v/v ethyl acetate/pet ether) to give **230b** as a colourless oil (1.54 g, 4.90 mmol, 44 %); ν_{max} 3349, 3072, 2931, 2858, 1712, 1590, 1472, 1428, 1390, 1361, 1264, 1189, 1106, 1083, 1008, 998, 965, 822, 735, 688 and 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.68 (4 H, dd, *J* 7.6, 1.3, 4 x Ar-*H*), 7.47-7.33 (6 H, m, 6 x Ar-*H*), 3.93-3.77 (4 H, m, C*H*$_2$CH$_2$CH$_2$OH + CH$_2$CH$_2$C*H*$_2$OH), 2.70 (1 H, br s, O*H*), 1.81 (2 H, quin, *J* 5.3, CH$_2$C*H*$_2$CH$_2$OH) and 1.06 (9 H, s, 3 x C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 135.59 (4 x *C*H), 133.29 (2 x *C*), 129.82 (2 x *C*H), 127.79 (4 x *C*H), 63.28 (*C*H$_2$), 61.94 (*C*H$_2$), 34.31 (*C*H$_2$), 26.86 (3 x *C*H$_3$) and 19.11 ((CH$_3$)$_3$*C*); *m/z* (ESI-MS) 337.1 $[M+Na]^+$. Found (ESI-HR-MS): 337.1587 $[M+Na]^+$, $C_{19}H_{26}NaO_2Si$ requires 337.1594 (2.0 ppm error). The data matched that previously reported for this compound.

Synthesis of 3-((*tert*-butyldiphenylsilyl)oxy)propanal (231b).

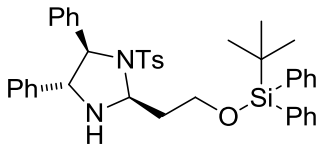


This is a known compound and has been fully characterised.[33g]

The solution of oxalylchloride (2M in DCM, 3.2 cm^3, 6.37 mmol) in anhydrous DCM (6.8 cm^3) was cooled to -78 °C, and was slowly added a solution of dimethylsulfoxide (1.0 g, 0.90 cm^3, 12.74 mmol) in DCM (3.4 cm^3) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 3-((*tert*-butyldiphenylsilyl)oxy)propan-1-ol **230b** (1.54 g, 4.90 mmol) in DCM (10.6 cm^3) was slowly added at the same temperature. After stirring for 40 min at -78 °C, Et_3N (3.0 g, 4.13 cm^3, 29.4 mmol) was added and the reaction mixture was allowed to warm up to rt. After 30 mins, water (21.2 cm^3) was added, and extracted with DCM, dried ($MgSO_4$), filtered and then

concentrated under vacuum to give the product as a orange oil **231b** (1.53 g, 4.90 mmol, >99 % quantitative conversion, includes traces of solvent); ν_{max} 3072, 2932, 2858, 1726, 1589, 1473, 1428, 1390, 1362, 1266, 1212, 1106, 1008, 998, 971, 875, 823, 737 and 701 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.81 (1 H, t, *J* 2.1, C*H*O), 7.66 (4 H, dd, *J* 7.8, 1.5, 4 x Ar-*H*), 7.46-7.34 (6 H, m, 6 x Ar-*H*), 4.01 (2 H, t, *J* 6.0, SiOCH_2), 2.60 (2 H, td, *J* 6.0, 2.1, CH_2CHO) and 1.04 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 201.91 (*C*H=O), 135.56 (4 x *C*H), 133.27 (2 x *C*), 129.84 (2 x *C*H), 127.80 (4 x *C*H), 58.31 (*C*H_2), 46.40 (*C*H_2), 26.77 (3 x *C*H_3) and ((CH_3)$_3$*C*); *m/z* (ESI-MS) 335.1 $[M+Na]^+$. Found (ESI-HR-MS): 367.1707 $[M+MeOH+Na]^+$, $C_{20}H_{28}NaO_3Si$ requires 367.1700 (-2.0 ppm error). The data matched that previously reported for this compound.

Synthesis of (2*S*,4*R*,5*R*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4,5-diphenyl-1-tosylimidazolidine (232b).

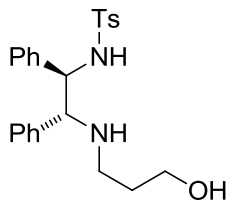


This compound is novel.

To a suspension of powdered molecular sieves (4 Å, 1.2 g) in dry methanol (70 cm^3) was added 3-((*tert*-butyldiphenylsilyl)oxy)propanal **231b** (1.53 g, 4.90 mmol), (1*R*, 2*R*)-TsDPEN (2.0 g, 5.44 mmol) and glacial acetic acid (14 drops). The reaction mixture was stirred at rt and monitored by TLC. After 2 hrs, the imine had formed, and sodium cyanoborohydride (0.92 g, 14.70 mmol) was added. The reaction was left to stir overnight at rt. Molecular sieves were removed by filtration, and the solution was concentrated under reduced pressure. The residue was re-dissolved in DCM (90 cm^3). The organic phase was washed with saturated $NaHCO_3$ (90 cm^3) and brine (90 cm^3),

dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **232b** as a white solid (1.12 g, 1.70 mmol, 35 %); Mp 64-67 °C; $[\alpha]_D^{22}$ -64 (*c* 0.5, $CHCl_3$); ν_{max} 3322, 3030, 2930, 2856, 1600, 1495, 1472, 1450, 1428, 1349, 1305, 1258, 1163, 1091, 1028, 949, 821, 736, 698 and 664 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.72-7.66 (4 H, m, 4 x Ar-*H*), 7.60 (2 H, d, *J* 8.2, 2 x Ar-*H*), 7.46-7.33 (6 H, m, 6 x Ar-*H*), 7.31-7.12 (10 H, m, 10 x Ar-*H*), 6.94 (2 H, d, *J* 6.6, 2 x Ar-*H*), 5.18 (1 H, d, *J* 7.2, NTsC*H*NH), 4.62 (1 H, d, *J* 6.3, C*H*NTs), 4.21 (1 H, br s, C*H*NH), 4.02-3.93 (1 H, m, $CH_{(1)}H_{(2)}$OSi), 3.92-3.84 (1 H, m, $CH_{(1)}H_{(2)}$OSi), 2.54 (1 H, br s, N*H*), 2.49-2.37 (1 H, m, $CHCH_{(1)}H_{(2)}$), 2.40 (3 H, s, CH_3Ts), 2.09-1.98 (1 H, m, $CHCH_{(1)}H_{(2)}$) and 1.06 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 143.57 (*C*), 140.41 (*C*), 138.45 (*C*), 135.65 (2 x *C*H), 135.61 (2 x *C*H), 134.52 (*C*), 133.63 (*C*), 133.58 (*C*), 129.71 (*C*H), 129.69 (*C*H), 129.59 (2 x *C*H), 128.59 (2 x *C*H), 128.45 (2 x *C*H), 127.79 (2 x *C*H), 127.72 (4 x *C*H), 127.64 (*C*H), 127.43 (*C*H), 126.84 (2 x *C*H), 126.49 (2 x *C*H), 76.22 (*C*H), 71.05 (*C*H), 69.90 (*C*H), 60.98 (CH_2), 38.63 (CH_2), 26.88 (3 x CH_3), 21.55 (CH_3) and 19.21 ($(CH_3)_3C$); *m/z* (ESI-MS) 661.2 $[M+H]^+$, 683.2 $[M+Na]^+$. Found (ESI-HR-MS): 661.2920 $[M+H]^+$, $C_{40}H_{45}N_2O_3SSi$ requires 661.2915 (0.1 ppm error).

Synthesis of *N*-((1*R*,2*R*)-2-((3-hydroxypropyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (234).

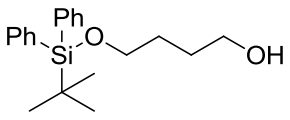


This compound is novel.

(2*S*,4*R*,5*R*)-2-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-4,5-diphenyl-1-tosylimidazolidine **232b** (143 mg, 0.22 mmol) in THF (0.32 cm^3) was added dropwise to a solution of

$LiAlH_4$ (25 mg, 122.52 mmol) in THF (1.4 cm^3) with stirring at 0 °C. After addition, the solution was allowed to stir at rt over the weekend. The solution was then cooled to 0 °C and quenched with a 50 : 50 mixture of water and THF (0.32 cm^3: 0.32 cm^3), followed by water (0.32 cm^3). Rochelle salt (216 g, 0.77 mmol) was then added followed by DCM (0.40 cm^3) and was further allowed to stir for 3 hrs. The remaining solution was then filtered off through celite, dried ($MgSO_4$), filtered and concentrated to give the crude product, which was then purified by flash chromatography (10→30 % v/v ethyl acetate/pet ether) to give **234** as a white solid (22 mg, 0.05 mmol, 24 %); Mp 110-113 °C; $[\alpha]_D^{27}$ -12.8 (*c* 0.25, $CHCl_3$); ν_{max} 3274, 3029, 2922, 1599, 1495, 1454, 1321, 1184, 1153, 1091, 1052, 922, 845, 812, 758, 698 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40 (2 H, d, *J* 8.3, 2 x Ar-*H*), 7.16-7.11 (3 H, m, 3 x Ar-*H*), 7.05-6.92 (7 H, m, 7 x Ar-*H*), 6.84 (2 H, dd, *J* 8.0, 1.2, 2 x Ar-*H*), 4.35 (1 H, d, *J* 8.0, C*H*NHTs), 3.74 (1 H, d, *J* 8.0, C*H*NH), 3.73-3.64 (2 H, m, CH_2OH), 2.58-2.52 (2 H, m, CH_2NH), 2.31 (3 H, s, CH_3Ts) and 1.76-1.56 (2 H, m, CH_2CH_2OH); δ_C (101 MHz, $CDCl_3$) 142.80 (*C*), 138.56 (*C*), 137.91 (*C*), 137.11 (*C*), 129.14 (2 x *C*H), 128.37 (2 x *C*H), 127.94 (2 x *C*H), 127.75 (2 x *C*H), 127.65 (*C*H), 127.49 (2 x *C*H), 127.30 (*C*H), 127.09 (2 x *C*H), 67.94 (*C*H), 63.05 (*C*H), 62.34 (CH_2), 45.70 (CH_2), 31.72 (CH_2) and 21.42 (CH_3); *m/z* (ESI-MS) 425.1 $[M+H]^+$. Found (ESI-HR-MS): 425.1895 $[M+H]^+$, $C_{24}H_{29}N_2O_3S$ requires 425.1893 (-0.3 ppm error).

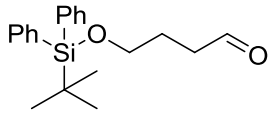
Synthesis of 4-((*tert*-butyldiphenylsilyl)oxy)butan-1-ol (230c).



This is a known compound and has been fully characterised.[28j]

To a solution of 1,4-butanediol (1.0 g, 1.0 cm^3, 11.1 mmol) and imidazole (1.0 g, 14.45 mmol) in dry DCM (35 cm^3) was added *tert*-butyl-chlorodiphenylsilane (6.1 g, 5.8 cm^3, 22.2 mmol) dropwise under a nitrogen atmosphere at rt followed by stirring at the same temperature for 4 hrs. The reaction mixture was then concentrated under reduced pressure and the residue was then purified by flash chromatography (1→9 % v/v ethyl acetate/pet ether) to give **230c** as a colourless oil (1.1 g, 3.35 mmol, 30 %); ν_{max} 3349, 3072, 2932, 2858, 1712, 1590, 1472, 1428, 1389, 1361, 1265, 1188, 1107, 998, 940, 861, 822, 793, 739, 700 and 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.67 (4 H, dd, *J* 7.7, 1.4, 4 x Ar-*H*), 7.46-7.33 (6 H, m, 6 x Ar-*H*), 3.70 (2 H, t, *J* 5.9, SiOCH_2), 3.66 (2 H, t, *J* 5.9, CH_2OH), 2.4 (1 H, br s, O*H*), 1.75-1.60 (4 H, m, CH_2CH_2CH_2OH) and 1.05 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 135.60 (4 x *C*H), 133.67 (2 x *C*), 129.68 (2 x *C*H), 127.70 (4 x *C*H), 64.05 (*C*H_2), 62.85 (*C*H_2), 29.86 (*C*H_2), 29.30 (*C*H_2), 26.86 (3 x *C*H_3) and 19.20 ($(CH_3)_3C$); *m/z* (ESI-MS) 351.2 $[M+Na]^+$. Found (ESI-HR-MS): 351.1745 $[M+Na]^+$, $C_{20}H_{28}NaO_2Si$ requires 351.1751 (1.4 ppm error). The data matched that previously reported for this compound.

Synthesis of 4-((*tert*-butyldiphenylsilyl)oxy)butanal (231c).

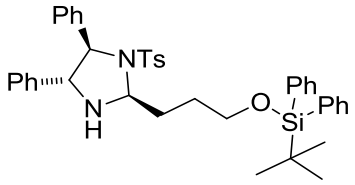


This is a known compound and has been fully characterised.[28j]

A solution of oxalylchloride (2M in DCM, 2.18 cm^3, 4.36 mmol) in anhydrous DCM (4.6 cm^3) was cooled to -78 °C, and was slowly added a solution of dimethylsulfoxide (0.68 g, 0.62 cm^3, 8.71 mmol) in DCM (2.3 cm^3) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 4-((*tert*-butyldiphenylsilyl)oxy)butan-1-ol **230c** (1.1 g, 3.35 mmol) in DCM (7.3 cm^3) was slowly added at the same temperature.

After stirring for 40 min at -78 °C, Et_3N (2.1 g, 2.82 cm^3, 20.1 mmol) was added and the reaction mixture was allowed to warm up to rt. After 30 mins, water (14.5 cm^3) was added, and the mixture was extracted with DCM, dried ($MgSO_4$), filtered and then concentrated under vacuum to give the product as a orange oil **231c** (1.1 g, 3.37 mmol, >99 % quantitative conversion, includes traces of solvent); ν_{max} 3072, 2932, 2858, 1724, 1472, 1428, 1390, 1110, 1008, 822, 737 and 701 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.79 (1 H, t, *J* 1.5, C*H*O), 7.64 (4 H, dd, *J* 7.8, 1.5, 4 x Ar-*H*), 7.46-7.35 (6 H, m, 6 x Ar-*H*), 3.69 (2 H, t, *J* 6.0, SiOCH_2), 2.55 (2 H, td, *J* 7.2, 1.6, CH_2CHO), 1.89 (2 H, quin, *J* 6.0, CH_2CH_2CHO) and 1.04 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 202.57 (*C*HO), 135.56 (4 x *C*H), 133.61 (2 x *C*), 129.70 (2 x *C*H), 127.71 (4 x *C*H), 62.93 (*C*H_2), 40.78 (*C*H_2), 26.84 (3 x *C*H_3), 25.27 (*C*H_2) and 19.20 ((CH_3)$_3$*C*); *m/z* (ESI-MS) 349.1 $[M+Na]^+$. Found (ESI-HR-MS): 327.1781 $[M+H]^+$, $C_{20}H_{27}O_2Si$ requires 327.1775 (-1.7 ppm error). The data matched that previously reported for this compound.

(2*S*,4*R*,5*R*)-2-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-4,5-diphenyl-1-tosylimidazolidine (232c).

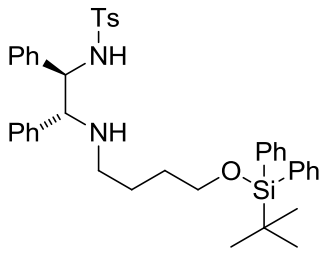


This compound is novel.

To a stirred solution of (*R*,*R*)-TsDPEN **81** (117 mg, 0.32 mmol) and molecular sieves (4 Å, 221 g) in dry methanol (2.5 cm^3) was added a solution of 4-((*tert*-butyldiphenylsilyl)oxy)butanal **231c** (125 mg, 0.38 mmol) in methanol (1.0 cm^3) followed by the addition of glacial acetic acid (0.022 cm^3). The reaction was stirred for 4 hrs during which time a white precipitate formed. The precipitate (molecular sieves

and the product) was filtered off and washed with cold methanol. The remaining solid was washed thoroughly with DCM to separate the product from molecular sieves, and was then concentrated *in vacuo*. Aminal **232c** was obtained as a white solid (78 mg, 0.12 mmol, 36 %); Mp 45-47 °C; $[\alpha]_D^{25}$ -45.6 (*c* 0.5, $CHCl_3$); ν_{max} 3069, 2930, 2857, 1600, 1495, 1472, 1449, 1428, 1349, 1304, 1163, 1091, 1029, 867, 821, 758, 741, 698 and 664 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.71-7.65 (4 H, m, 4 x Ar-*H*), 7.60 (2 H, d, *J* 8.2, 2 x Ar-*H*), 7.46-7.32 (6 H, m, 6 x Ar-*H*), 7.27-7.14 (10 H, m, 10 x Ar-*H*), 6.88 (2 H, d, *J* 6.7, 2 x Ar-*H*), 5.01 (1 H, dd, *J* 8.5, 5.2, NTsC*H*NH), 4.59 (1 H, d, *J* 6.8, C*H*NTs), 4.22 (1 H, d, *J* 6.8, C*H*NH), 3.77 (2 H, t, *J* 6.1, CH_2OSi), 2.40 (3 H, s, CH_3Ts), 2.31-2.13 (2 H, m, C$H_{(1)}$H$_{(2)}$CH$_2$OSi + N*H*), 2.02-1.88 (1 H, m, CH$_{(1)}H_{(2)}$CH$_2$OSi), 1.87-1.76 (2 H, m, CHCH_2) and 1.06 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 143.62 (*C*), 140.10 (*C*), 138.15 (*C*), 135.63 (3 x *C*H), 135.03 (*C*), 133.99 (*C*), 133.93 (*C*), 129.64 (2 x *C*H), 129.59 (*C*H), 128.71 (2 x *C*H), 128.43 (2 x *C*H), 127.88 (*C*H), 127.76 (2 x *C*H), 127.68 (3 x *C*H), 127.67 (3 x *C*H), 127.40 (*C*H), 126.90 (2 x *C*H), 126.45 (2 x *C*H), 78.75 (*C*H), 70.81 (*C*H), 70.48 (*C*H), 63.48 (*C*H_2), 33.20 (*C*H_2), 29.22 (*C*H_2), 26.92 (3 x *C*H_3), 21.55 (*C*H_3) and 19.27 ((CH$_3$)$_3$*C*); *m/z* (ESI-MS) 675.2 $[M+H]^+$, 697.2 $[M+Na]^+$. Found (ESI-HR-MS): 675.3082 $[M+H]^+$, $C_{41}H_{47}N_2O_3SSi$ requires 675.3071 (-1.5 ppm error).

Synthesis of *N*-((1*R*,2*R*)-2-((4-((*tert*-butyldiphenylsilyl)oxy)butyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (235).

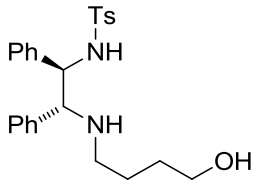


This compound is novel.

To a suspension of powdered molecular sieves (4 Å, 0.8 g) in dry methanol (48 cm^3) was added 4-((*tert*-butyldiphenylsilyl)oxy)butanal **231c** (1.1 g, 3.35 mmol), (1*R*,2*R*)-TsDPEN **81** (1.36 g, 3.72 mmol) and glacial acetic acid (10 drops). The reaction mixture was stirred at rt and monitored by TLC. After 2 hrs, the imine had formed, and sodium cyanoborohydride (0.63 g, 10.05 mmol) was added. The reaction was left to stir overnight at rt. Molecular sieves were removed by filtration, and the solution was concentrated under reduced pressure. The residue was re-dissolved in DCM (64 cm^3). The organic phase was washed with saturated $NaHCO_3$ (64 cm^3) and brine (64 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product, which after purification by flash chromatography (10→30 % v/v ethyl acetate/pet ether) gave **235** as a colourless gum (0.9 g, 1.33 mmol, 40 %); $[\alpha]_D^{23}$ -8.8 (*c* 0.5, $CHCl_3$); ν_{max} 3262, 3030, 2930, 2857, 1737, 1600, 1495, 1472, 1455, 1428, 1390, 1328, 1185, 1154, 1108, 1091, 1027, 998, 927, 812, 771, 740, 698 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.63 (4 H, d, *J* 7.5, 4 x Ar-*H*), 7.47-7.33 (8 H, m, 8 x Ar-*H*), 7.18-6.98 (8 H, m, 8 x Ar-*H*), 6.94 (2 H, d, *J* 7.5, 2 x Ar-*H*), 6.91-6.85 (2 H, m, 2 x Ar-*H*), 6.30 (1 H, br s, N*H*Ts), 4.23 (1 H, d, *J* 7.9, C*H*NHTs), 3.64-3.54 (3 H, m, C*H*NH + CH_2OSi), 2.42-2.34 (1 H, m, C$H_{(1)}$H$_{(2)}$NH), 2.32 (3 H, s, CH_3Ts), 2.30-2.22 (1 H, m, CH$_{(1)}H_{(2)}$NH), 1.54-1.38 (4 H, m, CH_2CH_2CH$_2$OSi) and 1.03 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 142.67 (*C*), 139.35 (*C*), 138.40 (*C*), 137.10 (*C*), 135.57 (4 x *C*H), 133.99 (2 x *C*), 129.58 (2 x *C*H), 129.08 (2 x *C*H), 128.32 (2 x *C*H), 127.91 (2 x *C*H), 127.64 (4 x *C*H), 127.59 (2 x *C*H), 127.45 (*C*H), 127.38 (2 x *C*H), 127.26 (*C*H), 127.15 (2 x *C*H), 67.79 (*C*H), 63.61 (*C*H_2), 63.06 (*C*H), 47.00 (*C*H_2), 30.11 (*C*H_2), 26.90 (3 x *C*H_3), 26.45 (*C*H_2), 21.45 (*C*H_3) and 19.23 ((CH$_3$)$_3$*C*); *m/z* (ESI-MS) 677.2 $[M+H]^+$, 699.2 $[M+Na]^+$.

Found (ESI-HR-MS): 677.3231 $[M+H]^+$, $C_{41}H_{49}N_2O_3SSi$ requires 677.3228 (-0.3 ppm error).

Synthesis of *N*-((1*R*,2*R*)-2-((4-hydroxybutyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (236).

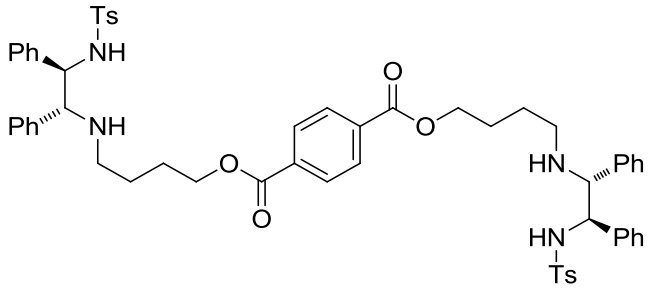


This compound is novel.

To a solution of *N*-((1*R*,2*R*)-2-((4-((*tert*-butyldiphenylsilyl)oxy)butyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **235** (730 mg, 1.08 mmol) in dry THF (7 cm^3) was added TBAF (1 M solution in THF, 1.62 cm^3, 1.62 mmol) at 0 °C. The resulting mixture was stirred at rt for 24 hrs. The reaction mixture was then concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography (10→100 % v/v ethyl acetate/pet ether) to give **236** as a white solid (360 mg, 0.82 mmol, 76 %); Mp 135-138 °C; $[\alpha]_D^{22}$ -12.8 (*c* 0.25, $CHCl_3$); ν_{max} 3278, 3091, 2836, 1598, 1495, 1450, 1429, 1350, 1333, 1259, 1215, 1189, 1181, 1156, 1090, 1060, 1046, 1030, 1011, 996, 962, 922, 903, 843, 832, 820, 773, 757, 727, 698 and 668 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39 (2 H, d, *J* 8.2, 2 x Ar-*H*), 7.15-7.10 (3 H, m, 3 x Ar-*H*), 7.08-6.97 (5 H, m, 5 x Ar-*H*), 6.96-6.91 (2 H, m, 2 x Ar-*H*), 6.88 (2 H, d, *J* 6.9, 2 x Ar-*H*), 4.30 (1 H, d, *J* 8.0, C*H*NHTs), 3.67 (1 H, d, *J* 8.0, C*H*NH), 3.64-3.55 (2 H, m, CH_2OSi), 2.50-2.34 (2 H, m, CH_2NH), 2.32 (3 H, s, CH_3Ts) and 1.60-1.40 (4 H, m, CH_2CH_2CH_2OSi); δ_C (101 MHz, $CDCl_3$) 142.80 (*C*), 138.98 (*C*), 138.13 (*C*), 137.04 (*C*), 129.13 (2 x *C*H), 128.31 (2 x *C*H), 127.93 (2 x *C*H), 127.59 (2 x *C*H), 127.52 (3 x *C*H), 127.29 (*C*H), 127.14 (2 x *C*H), 67.82 (*C*H), 63.04 (*C*H), 62.62 (*C*H_2), 47.01

(CH_2), 30.72 (CH_2), 26.79 (CH_2) and 21.44 (CH_3); *m/z* (ESI-MS) 439.1 $[M+H]^+$, 461.1 $[M+Na]^+$. Found (ESI-HR-MS): 439.2050 $[M+H]^+$, $C_{25}H_{31}N_2O_3S$ requires 439.2050 (-0.5 ppm error).

Synthesis of bis(4-(((1*R*,2*R*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)amino)butyl) terephthalate (243).

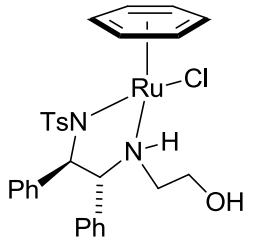


This compound is novel.

Terephthalic acid (11 mg, 0.065 mmol) was added to a solution of *N*-((1*R*,2*R*)-2-((4-hydroxybutyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **236** (57 mg, 0.13 mmol) in DCM (2 cm^3) at rt, followed by addition of EDC (153 mg, 0.80 mmol) and DMAP (16 mg, 0.13 mmol). The resulting mixture was stirred overnight and then water (2 cm^3) was added. The organic phase was separated from the aqueous, and then DCM (2 x 2 cm^3) was further added to extract the remaining product from the aqueous. The organic layers were then combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure giving the crude product, which was then purified by flash chromatography (10→30 % v/v ethyl acetate/pet ether) giving **243** as white crystals (20 mg, 0.02 mmol, 31 %); Mp 199-202 °C; $[\alpha]_D^{27}$ -12.8 (*c* 0.25, $CHCl_3$); ν_{max} 3267, 2931, 1716, 1600, 1495, 1454, 1408, 1325, 1269, 1184, 1154, 1117, 1093, 1018, 928, 875, 843, 812, 762, 731, 698 and 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.04 (4 H, s, 4 x CO_2Ar-*H*), 7.37 (4 H, d, *J* 8.0, 2 x Ar-*H*), 7.16-7.08 (6 H, m, 6 x Ar-*H*), 7.07-6.97 (10 H, m, 10

x Ar-*H*), 6.96-6.88 (8 H, m, 8 x Ar-*H*), 4.34-4.24 (6 H, m, 2 x C*H*NHTs + 2 x CH_2OC=O), 3.65 (2 H, d, *J* 8.0, 2 x C*H*NH), 2.52-2.42 (2 H, m, 2 x C$H_{(1)}$H$_{(2)}$NH), 2.41-2.33 (2 H, m, 2 x CH$_{(1)}H_{(2)}$NH), 2.31 (6 H, s, 2 x CH_3Ts), 1.80-1.65 (4 H, m, 2 x CH$_2$CH_2CH$_2$OC=O) and 1.63-1.45 (4 H, m, 2 x CH_2CH$_2$CH$_2$OC=O); δ_C (101 MHz, $CDCl_3$) 165.82 (2 x *C*=O), 142.74 (2 x *C*), 139.16 (2 x *C*), 138.24 (2 x *C*), 137.06 (2 x *C*), 134.10 (2 x *C*), 129.57 (4 x *C*H), 129.10 (4 x *C*H), 128.36 (4 x *C*H). 127.93 (4 x *C*H), 127.55 (6 x *C*H), 127.42 (4 x *C*H), 127.29 (2 x *C*H), 127.12 (4 x *C*H), 67.87 (2 x *C*H), 65.17 (2 x *C*H_2), 63.11 (2 x *C*H), 46.76 (2 x *C*H_2), 26.58 (2 x *C*H_2), 26.37 (2 x *C*H_2) and 21.43 (2 x *C*H_3); *m/z* (ESI-MS) 1007.2 $[M+H]^+$, 1029.1 $[M+Na]^+$. Found (ESI-HR-MS): 504.2095 $[M+2H]^{2+}$, $C_{58}H_{64}N_4O_8S_2$ requires 504.2077 (-2.1 ppm error).

Synthesis of catalyst (244).

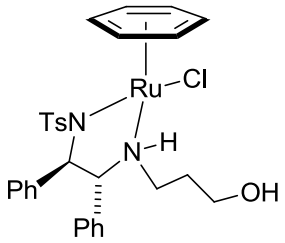


This compound is novel.

A mixture of benzeneruthenium (II) chloride dimer (40 mg, 0.08 mmol), *N*-((1*R*,2*R*)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **233** (46 mg, 0.11 mmol) and triethylamine (0.06 cm^3, 0.43 mmol) in IPA (2.4 cm^3) was heated at 80 °C for 1 hr. The solution was then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (4.8 cm^3) and then washed with water (2.4 cm^3) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na_2SO_4), filtered and then concentrated under reduced pressure giving **244** as a brown solid (58 mg, 0.09 mmol, 85 %); Mp 250-253 °C (dec); $[\alpha]_D^{27}$ +120 (*c* 0.02, $CHCl_3$);

ν_{max} 3435, 3063, 3030, 2917, 1730, 1599, 1494, 1453, 1435, 1398, 1266, 1128, 1084, 1059, 1003, 932, 834, 808, 749, 697 and 663 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.55-6.65 (14 H, m, 14 x Ar-*H*), 6.01 (6 H, s, 6 x Ar-*H*), 4.86 (1 H, d, *J* 10.3, C*H*NTs), 4.51 (1 H, d, *J* 10.3, C*H*NH), 3.80-3.40 (1 H, br m, $CH_{(1)}H_{(2)}OH$), 3.35-3.10 (1 H, br m, $CH_{(1)}H_{(2)}OH$), 2.50-2.25 (2 H, br m, CH_2NH) and 2.20 (3 H, s, CH_3Ts); δ_C (101 MHz, $CDCl_3$) 140.12 (*C*), 130.67 (*C*H), 128.84 (*C*H), 128.36 (5 x *C*H), 128.21 (*C*H), 127.63 (2 x *C*H), 126.86 (4 x *C*H), 83.67 (6 x *C*H), 82.89 (2 x *C*H), 74.28 (2 x CH_2) and 21.22 (CH_3); *m/z* (ESI-MS) 589.0 $[M\text{-}Cl]^+$. Found (ESI-HR-MS): 589.1106 $[M\text{-}Cl]^+$, $C_{29}H_{31}N_2O_3{}^{102}RuS$ requires 589.1100 (-0.3 ppm error).

Synthesis of catalyst (245).

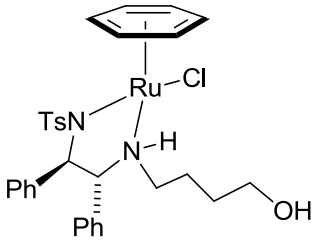


This compound is novel.

A mixture of benzeneruthenium(II) chloride dimer (13 mg, 0.025 mmol), *N*-((1*R*,2*R*)-2-((3-hydroxypropyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **234** (14 mg, 0.033 mmol) and triethylamine (0.018 cm^3, 0.13 mmol) in IPA (0.75 cm^3) was heated at 80 °C for 1 hr. The solution was then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (1.5 cm^3) and then washed with water (0.75 cm^3) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na_2SO_4), filtered and then concentrated under reduced pressure giving **245** as a brown solid (13.4 mg, 0.02 mmol, 64 %); Mp 210-213 °C (dec); $[\alpha]_D{}^{27}$ -360 (*c* 0.02, $CHCl_3$); ν_{max} 3436, 3204, 3064, 3029, 2922, 2853, 1730, 1600, 1494, 1454, 1437, 1381,

1267, 1185, 1128, 1083, 1054, 1004, 912, 812, 759, 698, 682 and 658 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30-6.50 (14 H, m, 14 x Ar-*H*), 5.90 (6 H, s, 6 x Ru-Ar-*H*), 4.18-4.05 (1 H, br m, C*H*NTs), 3.99-3.86 (1 H, br m, C*H*NH), 3.68-3.58 (1 H, br m, $CH_{(1)}H_{(2)}OH$), 3.57-3.46 (1 H, br m, $CH_{(1)}H_{(2)}OH$), 3.16-3.04 (1 H, br m, $CH_{(1)}H_{(2)}NH$), 2.96-2.82 (1 H, br m, $CH_{(1)}H_{(2)}NH$), 2.22 (3 H, s, CH_3Ts), 2.12-2.01 (2 H, br m, CH_2CH_2OH) and 1.41-1.33 (1 H, br m, N*H*); δ_C (101 MHz, $CDCl_3$) 141.50 (*C*), 139.64 (*C*), 139.54 (*C*), 136.91 (*C*), 128.60 (2 x *C*H), 128.50 (2 x *C*H), 128.17 (*C*H), 128.07 (4 x *C*H), 127.54 (2 x *C*H), 127.06 (2 x *C*H), 126.37 (*C*H), 84.72 (6 x *C*H), 81.43 (*C*H), 69.84 (*C*H), 61.27 (CH_2), 53.62 (CH_2), 29.70 (CH_2) and 21.23 (CH_3); *m/z* (ESI-MS) 603.0 $[M\text{-}Cl]^+$. Found (ESI-HR-MS): 603.1259 $[M\text{-}Cl]^+$, $C_{30}H_{33}N_2O_3{}^{102}RuS$ requires 603.1257 (0.1 ppm error).

Synthesis of catalyst (246).

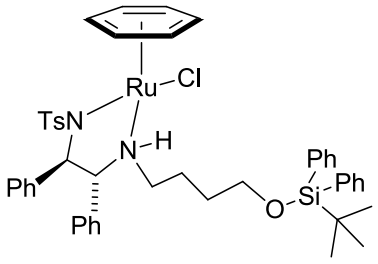


This compound is novel.

A mixture of benzeneruthenium(II) chloride dimer (28 mg, 0.056 mmol), *N*-((1*R*,2*R*)-2-((4-hydroxybutyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **236** (32 mg, 0.074 mmol) and triethylamine (0.04 cm^3, 0.29 mmol) in IPA (2.2 cm^3) was heated at 80 °C for 1 hr. The solution was then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (4.4 cm^3) and then washed with water (2.2 cm^3) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na_2SO_4), filtered and then concentrated under reduced pressure giving **246** as orange

brown crystals (43 mg, 0.07 mmol, 89 %); Mp 220-223 °C (dec); $[\alpha]_D^{26}$ -480 (*c* 0.02, $CHCl_3$); ν_{max} 3428, 3062, 2863, 1599, 1494, 1455, 1437, 1385, 1267, 1127, 1083, 1054, 992, 915, 809, 750, 697, 681 and 656 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (2 H, d, *J* 7.8, 2 x Ar-*H*), 7.15-7.00 (3 H, m, 3 x Ar-*H*), 6.80 (3 H, d, *J* 7.8, 3 x Ar-*H*), 6.75-6.64 (4 H, m, 4 x Ar-*H*), 6.56 (2 H, d, *J* 6.8, 2 x Ar-*H*), 5.90 (6 H, s, 6 x Ar-Ru-*H*), 3.99 (1 H, t, *J* 10.2, C*H*NTs), 3.92 (1 H, t, *J* 10.2, C*H*NH), 3.76 (1 H, br m, CHN*H*), 3.60 (2 H, br m, CH_2OH), 3.44-3.30 (1 H, br m, $CH_{(1)}H_{(2)}NH$), 2.85-2.65 (1 H, br m, $CH_{(1)}H_{(2)}NH$), 2.22 (3 H, s, CH_3Ts), 2.16-1.98 (1 H, br m, $CH_{(1)}H_{(2)}CH_2NH$), 1.80-1.66 (1 H, br m, $CH_{(1)}H_{(2)}CH_2NH$), 1.64-1.48 (1 H, br m, $CH_{(1)}H_{(2)}CH_2OH$) and 1.43-1.29 (1 H, br m, $CH_{(1)}H_{(2)}CH_2OH$); δ_C (101 MHz, $CDCl_3$) 141.80 (*C*), 139.57 (*C*), 139.45 (*C*), 137.10 (*C*), 128.66 (2 x *C*H), 128.56 (2 x *C*H), 128.24 (*C*H), 128.06 (4 x *C*H), 127.43 (2 x *C*H), 127.04 (2 x *C*H), 126.32 (*C*H), 86.64 (6 x *C*H), 80.89 (*C*H), 69.61 (*C*H), 61.62 (CH_2), 54.82 (CH_2), 29.83 (CH_2), 25.43 (CH_2) and 21.23 (CH_3); *m/z* (ESI-MS) 617.0 $[M-Cl]^+$. Found (ESI-HR-MS): 617.1414 $[M-Cl]^+$, $C_{31}H_{35}N_2O_3{}^{102}RuS$ requires 617.1406 (-2.03 ppm error).

Synthesis of catalyst (247).



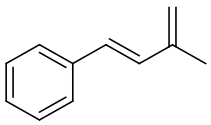
This compound is novel.

A mixture of benzeneruthenium(II) chloride dimer (28 mg, 0.056 mmol), *N*-((1*R*,2*R*)-2-((4-((*tert*-butyldiphenylsilyl)oxy)butyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **235** (50 mg, 0.074 mmol) and triethylamine (0.04 cm^3, 0.29

mmol) in IPA (2.2 cm^3) was heated at 80 °C for 1 hr. The solution was then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (4.4 cm^3) and then washed with water (2.2 cm^3) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na_2SO_4), filtered and then concentrated under reduced pressure giving **247** as orange brown crystals (58 mg, 0.07 mmol, 88 %); Mp 205-208 °C (dec); $[\alpha]_D^{26}$ -240 (*c* 0.02, $CHCl_3$); ν_{max} 3067, 2930, 2856, 1600, 1494, 1455, 1428, 1387, 1361, 1262, 1189, 1126, 1108, 1083, 992, 915, 822, 759, 728, 697 and 657 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.60 (4 H, d, *J* 7.2, 4 x Ar-*H*), 7.45-7.25 (6 H, m, 6 x Ar-*H*), 7.13-6.99 (4 H, m, 4 x Ar-*H*), 6.90-6.79 (4 H, m, 4 x Ar-*H*), 6.74 (2 H, t, *J* 7.2, 2 x Ar-*H*), 6.65 (2 H, d, *J* 6.5, 2 x Ar-*H*), 6.59 (2 H, d, *J* 7.2, 2 x Ar-*H*), 5.79 (6 H, s, 6 x Ar-*H*), 3.97 (1 H, d, *J* 10.3, C*H*NHTs), 3.84 (1 H, t, *J* 11.4, C*H*NH), 3.70 (1 H, t, *J* 11.4, CHN*H*), 3.61-3.50 (2 H, m, CH_2OSi), 3.30-3.10 (1 H, br m, C$H_{(1)}H_{(2)}$NH), 2.85-2.70 (1 H, br m, C$H_{(1)}H_{(2)}$NH), 2.22 (3 H, s, CH_3Ts), 2.15-2.01 (1 H, br m, C$H_{(1)}H_{(2)}CH_2$NH), 1.72-1.60 (1 H, br m, C$H_{(1)}H_{(2)}CH_2$NH), 1.58-1.46 (1 H, br m, C$H_{(1)}H_{(2)}CH_2$OSi), 1.42-1.27 (1 H, br m, C$H_{(1)}H_{(2)}CH_2$OSi) and 1.03 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 141.54 (*C*), 139.83 (*C*), 139.46 (*C*), 137.01 (*C*), 133.55 (4 x *C*H), 133.76 (*C*), 133.62 (*C*), 129.72 (2 x *C*H), 128.68 (2 x *C*H), 128.59 (2 x *C*H), 128.27 (*C*H), 128.01 (2 x *C*H), 127.77 (5 x *C*H), 127.68 (2 x *C*H), 127.46 (*C*H), 127.04 (2 x *C*H), 126.37 (*C*H), 84.51 (6 x *C*H), 81.05 (*C*H), 69.67 (*C*H), 63.16 (*C*H_2), 54.88 (*C*H_2), 30.12 (*C*H_2), 27.00 (3 x *C*H_3), 25.39 (*C*H_2), 21.26 (*C*H_3) and 19.25 ($(CH_3)_3C$); *m/z* (ESI-MS) 855.0 $[M\text{-}Cl]^+$. Found (ESI-HR-MS): 855.2596 $[M\text{-}Cl]^+$, $C_{47}H_{53}N_2O_3{}^{102}RuSSi$ requires 855.2584 (0.13 ppm error).

4.4 Procedures from Section 2.4.

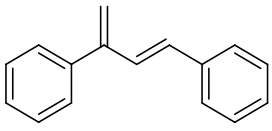
Synthesis of (*E*)-(3-Methylbuta-1,3-dien-1-yl)benzene (278).



This is a known compound and has been fully characterised.

To a solution of methyltriphenylphosphonium bromide (3.93 g, 11.0 mmol) in 1,4-dioxane (100 cm^3), was added sodium hexamethyldisilazide (2.02 g, 11.0 mmol). The resulting yellow mixture was stirred for 1 hour at 60 °C. 4-Phenyl-3-buten-2-one (1.50 g, 10.0 mmol) was then added and the solution was stirred at 60 °C until completion. The reaction was completed after 4 hrs as shown by TLC analysis, after which the solution was concentrated under reduced pressure, and purified by flash chromatography (pentane : diethyl ether/ 99 : 1) giving **278** as a colourless oil (720 mg, 5.00 mmol, 50 %); δ_H (400 MHz, $CDCl_3$) 7.43 (2 H, d, *J* 7.8, 2 x Ar-*H o* to C=C), 7.31 (2 H, d, *J* 7.8, 2 x Ar-*H m* to C=C), 7.25-7.19 (1 H, m, Ar-*H p* to C=C), 6.88 (1 H, d, *J* 16.1, C*H*=CH *cis* to Ar ring), 6.53 (1 H, d, J 16.1, CH=C*H cis* to $C(CH_3)=CH_2$), 5.11 (1 H, s, $C(CH_3)=CH_{(1)}H_{(2)}$), 5.07 (1 H, s, $C(CH_3)=CH_{(1)}H_{(2)}$) and 1.97 (3 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 142.07 (*C*), 137.41 (*C*), 131.71 (*C*H), 128.70 (*C*H), 128.62 (2 x *C*H), 127.44 (*C*H), 126.49 (2 x *C*H), 117.37 (CH_2) and 18.62 (CH_3). The data matched that previously reported for this compound.

Synthesis of (*E*)-buta-1,3-diene-1,3-diyldibenzene (279).

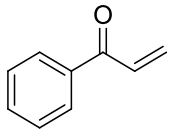


This is a known compound and has been fully characterised.[33i]

To a solution of methyltriphenylphosphonium bromide (3.93 g, 11.0 mmol) in 1,4-dioxane (100 cm^3), was added sodium hexamethyldisilazide (2.02 g, 11.0 mmol). The

resulting yellow mixture was stirred for 1 hour at 60 °C. 1,3-Diphenyl-2-propenone (2.10 g, 10.0 mmol) was then added and the solution was stirred at 60 °C until completion. The reaction was completed after 4 hrs as shown by TLC analysis, after which the solution was concentrated under reduced pressure, and purified by flash chromatography (pentane : ethyl acetate/ 99 : 1) giving **279** as a colourless oil (241 mg, 1.17 mmol, 12 %); δ_H (400 MHz, $CDCl_3$) 7.45-7.20 (10 H, m, 10 x Ar-*H*), 7.05 (1 H, d, *J* 16.1, C*H*=CH), 6.49 (1 H, d, *J* 16.1, CH=C*H*), 5.42 (1 H, s, $CH_{(1)}H_{(2)}$=C) and 5.24 (1 H, d, *J* 1.6, $CH_{(1)}H_{(2)}$=C); δ_C (101 MHz, $CDCl_3$) 148.18 (*C*), 140.23 (*C*), 137.21 (*C*), 131.94 (*C*H), 130.38 (*C*H), 128.62 (2 x *C*H), 128.48 (2 x *C*H), 128.24 (2 x *C*H), 127.68 (*C*H), 127.57 (*C*H), 126.58 (2 x *C*H) and 117.39 (CH_2). The data matched that previously reported for this compound.

Synthesis of 1-phenylprop-2-en-1-one (273).



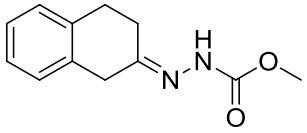
This is a known compound and has been fully characterised.[30a]

A mixture of 3-chloro-1-phenyl-1-propanone (2.0 g, 11.8 mmol) and AcOK (1.28 g, 13 mmol) in EtOH (100 cm^3) was stirred under reflux for 4 hrs. After stirring overnight at rt, the solvent was evaporated off under reduced pressure. The residue was dissolved in AcOEt (100 cm^3) and washed with H_2O (3 x 100 cm^3). Organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure giving the crude product, which was then purified by flash chromatography (pentane: ethyl acetate/ 20 : 1) giving **273** as a colourless oil (480 mg, 3.63 mmol, 31 %); δ_H (400 MHz, $CDCl_3$) 7.98 (2 H, m, 2 x Ar-*H o* to C=O), 7.58 (1 H, tt, *J* 7.4, 2.2, 1 x Ar-*H p* to C=O), 7.52-7.45 (2 H, m, 2 x Ar-*H m* to C=O), 7.17 (1 H, dd, *J* 17.1, 10.6, C*H*=CH_2), 6.44 (1 H, dd, *J* 17.1, 1.7,

CH=C*H*$_{(1)}$H$_{(2)}$) and 5.94 (1 H, dd, *J* 10.6, 1.7, CH=CH$_{(1)}$*H*$_{(2)}$); δ_C (101 MHz, $CDCl_3$) 191.07 (*C*=O), 137.28 (*C*), 133.00 (*C*H), 132.39 (*C*H), 130.21 (*C*H$_2$), 128.71 (2 x *C*H) and 128.63 (2 x *C*H). The data matched that previously reported for this compound.

4.5 Procedures from Section 3.1 (Appendix).

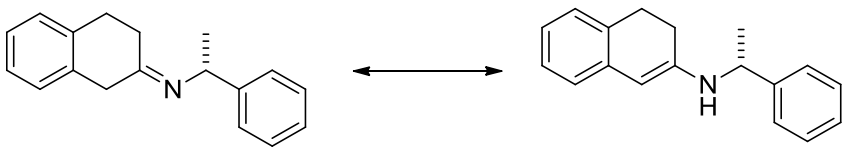
(*E*)-Methyl 2-(3,4-dihydronaphthalen-2(1*H*)-ylidene)hydrazinecarboxylate (296).



This is a known compound and has been fully characterised.[31e]

A solution of β-tetralone (1.46 g, 1.32 cm^3, 10.00 mmol) and methylhydrazinocarboxylate (0.90 g, 10.00 mmol) in MeOH (20 cm^3) was heated at 50 °C for 8 hrs, after which the reaction was stirred at rt for 5 days. The solution was then filtered through a filter paper leaving behind impurities, and the filtrate was then concentrated under reduced pressure giving **296** as a yellow solid (1.44 g, 6.60 mmol, 66 %); δ_H (400 MHz, $CDCl_3$) (*E*/*Z*) 7.18-7.02 (4 H, m, 4 x Ar-*H*), 3.90-3.75 (3 H, br m, OC*H*$_3$), 3.62 (0.8 H, br s C=CC*H*$_2$C=N), 3.59 (1.2 H, s, C=CC*H*$_2$C=N), 2.68 (2 H, q, *J* 5.6, C=CC*H*$_2$CH$_2$), 2.63 (1 H, t, *J* 5.6, C=CC*H*$_2$C*H*$_{(1)}$H$_{(2)}$) and 2.51-2.40 (1 H, br m, C=CC*H*$_2$CH$_{(1)}$*H*$_{(2)}$); δ_C (101 MHz, $CDCl_3$) (*E*/*Z*) 154.75 (*C*), 137.51 (*C*), 135.08 (*C*), 128.68 (*C*H), 128.28 (*C*H), 127.52 (*C*H), 127.00 (*C*H), 126.89 (*C*H), 50.56 (*C*H$_3$), 32.18 (*C*H$_2$), 30.41 (*C*H$_2$), 29.03 (*C*H$_2$), 27.56 (*C*H$_2$) and 25.53 (*C*H$_2$). The data matched that previously reported for this compound.

(*R*)-*N*-(1-Phenylethyl)-3,4-dihydronaphthalen-2-amine (297).

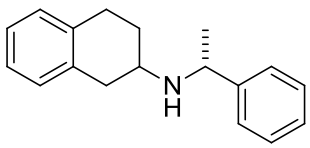


This is a known compound and has been fully characterised.[31g]

Synthesis of the imine from β-tetralone and (*R*)-(+)-α-methylbenzylamine; All solvents were dried and deoxygenated before use. Deoxygenation was carried out by passing a rapid stream of dry nitrogen through the dry solvent for ca. 15 min. Without this precaution highly coloured products were obtained. An oven-dried three-necked flask (100 cm^3) was equipped with a dropping funnel, a Herschberg stirrer, and a reflux condenser. The flask was purged with nitrogen prior to introduction of the reagents, and a positive pressure of nitrogen was maintained in the apparatus throughout the whole operation. The flask was charged with (*R*)-(+)-α-methylbenzylamine (1.21 g, 1.27 cm^3, 10.00 mmol), triethylamine (6.07 g, 3.36 cm^3, 60.00 mmol) and hexane (20 cm^3). The mixture was cooled ca. 5 °C by means of an ice bath and a solution of titanium (IV) chloride (1.52 g, 0.88 cm^3, 8.00 mmol) in hexane (10 cm^3) was added dropwise over a period of ca. 10 min. The precipitated titanium (IV) chloride-amine complexes were homogenized and suspended by vigorous stirring for a few minutes prior to introduction of the ketone. The vigorous stirring of the suspended complexes was maintained and a solution of β-tetralone (1.46 g, 1.32 cm^3, 10.00 mmol) in diethylether-hexane (1 : 1, 5 cm^3 : 5 cm^3) was added in one batch. The ice bath was removed and the reaction was cooled to rt and diethylether (40 cm^3) was added to precipitate the titanium complexes. Under a protective nitrogen atmosphere, the reaction mixture was filtered through a sintered glass filter. The solid material in the reaction flask and on the filter was rinsed with diethylether (4 x 10 cm^3). The solvent was removed under reduced pressure and the residual crude product was obtained as a dark green oil, and after purification by

Kugelrohr distillation (200 °C) **297** was obtained as yellow oil (0.88 g, 3.53 mmol, 36 %), which was stored under inert conditions; δ_H (300 MHz, $CDCl_3$) 7.35-6.68 (9 H, m, 9 x Ar-*H*), 5.03 (1 H, s, *H*C=CNH), 4.49 (1 H, q, *J* 6.4, C*H*CH_3), 3.58 (1 H, br s, N*H*), 2.80 (2 H, t, *J* 8.0, C$H_2$$CH_2$C(NH)=C), 2.30 (2 H, t, *J* 8.0, CH_2CH_2C(NH)=C) and 1.48 (3 H, d, *J* 6.4, CH_3); δ_C (75 MHz, $CDCl_3$) 144.79 (*C*), 144.61 (*C*), 137.40 (*C*), 130.85 (*C*), 128.60 (2 x *C*H), 126.92 (*C*H), 126.74 (*C*H), 126.48 (*C*H), 125.80 (2 x *C*H), 123.49 (*C*H), 122.40 (*C*H), 94.52 (*C*H), 52.79 (*C*H), 29.30 (CH_2), 28.49 (CH_2) and 24.29 (CH_3). The data matched that previously reported for this compound.

_N_-((_R_)-1-Phenylethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (301).

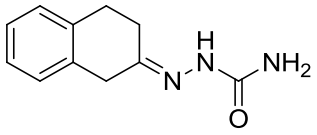


This compound is novel.

A solution of (*R*)-*N*-(1-Phenylethyl)-3,4-dihydronaphthalen-2-amine **297** (0.42 g, 1.69 mmol) with acetic acid (0.1 cm^3) in MeOH (3 cm^3) was stirred for an hour. Sodium cyanoborohydride (0.12 g, 1.69 mmol) was then added portionwise to the solution. The reaction mixture was stirred at rt until completion. After completion, the solution was concentrated under reduced pressure and water (5 cm^3) was added, and the product was then extracted with DCM (3 x 5 cm^3). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure, giving **301** as a colourless oil after distillation (0.35 g, 1.39 mmol, 83 %); δ_H (400 MHz, $CDCl_3$) 7.40-6.95 (9 H, m, 9 x Ar-*H*), 4.04 (1 H, q, *J* 6.6, C*H*CH_3), 3.12-2.50 (5 H, m, C$H_2$$CH_2$C*H*(NH)C$H_2$), 1.66-1.49 (2 H, m, CH_2CH_2CH(NH)CH_2) and 1.37 (3 H, d, *J* 6.6, CH_3); δ_C (101 MHz, $CDCl_3$) 145.94 (*C*), 136.36 (*C*), 136.31 (*C*), 128.54 (2 x *C*H), 128.52 (2 x *C*H), 126.93

(*C*H), 126.57 (4 x *C*H), 54.84 (*C*H), 50.53 (*C*H), 30.60 (*C*H_2), 28.98 (*C*H_2), 28.05 (*C*H_2) and 24.95 (*C*H_3); *m/z* (ESI-MS) 252.1 $[M+H]^+$.

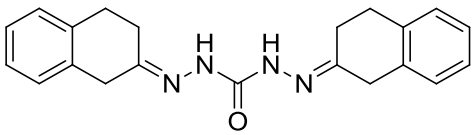
(*E*)-2-(3,4-Dihydronaphthalen-2(1H)-ylidene)hydrazinecarboxamide (298).



This is a known compound and has been fully characterised.[31g]

A mixture of semicarbazide hydrochloride (1.12 g, 10.00 mmol), sodium acetate (0.82 g, 10.00 mmol) and water (10 cm^3) was added slowly to a stirred solution of β-tetralone (1.46 g, 1.32 cm^3, 10.00 mmol) in ethanol (95 %, 30 cm^3). The reaction mixture was stirred at rt for 24 hrs. The precipitate was collected, washed with ether and water and dried. Recrystallization from ethanol (95 %) gave **298** as white crystals (1.42 g, 7.00 mmol, 70 %); ν_{max} 3437, 3186, 1682, 1580, 1462, 1423, 1411, 1267, 1204, 1178, 1137, 1108, 1137, 1108, 1074, 995, 948, 760, 751, 740 and 662 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.90 (1 H, s, N*H*), 7.25-7.16 (4 H, m, 4 x Ar-*H*), 6.25 (2 H, s, NH_2), 3.51 (2 H, s, $CH_2CH_2C(=N)CH_2$), 2.85 (2 H, t, *J* 6.6, $CH_2CH_2C(=N)CH_2$) and 2.46 (2 H, t, *J* 6.6, $CH_2CH_2C(=N)CH_2$); δ_C (101 MHz, DMSO-d_6) 157.32 (*C*=O), 150.15 (*C*=N), 138.19 (*C*), 135.70 (*C*), 127.05 (*C*H), 126.97 (*C*H), 126.37 (*C*H), 126.27 (*C*H), 37.68 (CH_2), 27.05 (CH_2) and 25.68 (CH_2); *m/z* (ESI-MS) 204.0 $[M+H]^+$, 226.0 $[M+Na]^+$. The data matched that previously reported for this compound.

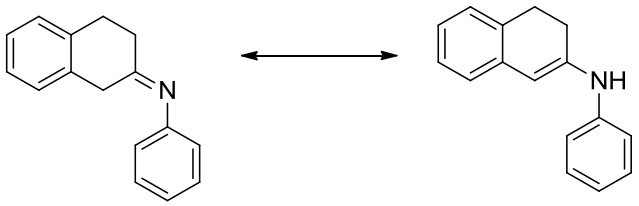
Compound (299).



This is a known compound and has been fully characterised.[31g]

A solution of carbohydrazine (0.90 g, 10.00 mmol) in MeOH (20 cm^3) was added to a solution of β-tetralone (2.92 g, 2.64 cm^3, 20.00 mmol) in MeOH (25 cm^3) and the resultant mixture was stirred at rt for 20 min. The solid was collected and recrystallization from ethanol (95 %) gave **299** as a white solid (1.59 g, 4.59 mmol, 46 %); δ_H (400 MHz, CD_3CN-d_3) 7.30-7.20 (8 H, m, 8 x Ar-*H*), 3.73-3.58 (4 H, m, 2 x $CH_2CH_2C(=N)CH_2$), 3.03-2.90 (4 H, m, 2 x $CH_2CH_2C(=N)CH_2$) and 2.70-2.50 m, 2 x $CH_2CH_2C(=N)CH_2$); *m/z* (ESI-MS) 347.1 $[M+H]^+$, 369.1 $[M+Na]^+$. The data matched that previously reported for this compound.

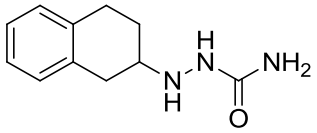
_N_-(3,4-Dihydronaphthalen-2(1*H*)-ylidene)aniline (300).



This compound is novel.

Procedure from **297** was used for the formation of **300** as a brown oil (1.66 g, 7.50 mmol, 75 %); δ_H (400 MHz, $CDCl_3$) 7.32-6.86 (9 H, m, 9 x Ar-*H*), 6.03 (1 H, s, C*H*=C-NH), 5.19 (1 H, br s, N*H*), 2.89 (2 H, t, *J* 8.4, $CH_2CH_2C(NH)=CH$) and 2.41 (2 H, t, *J* 8.4, $CH_2CH_2C(NH)=CH$); δ_C (101 MHz, $CDCl_3$) 141.74 (*C*), 141.37 (*C*), 136.41 (*C*), 131.72 (*C*), 129.28 (2 x *C*H), 126.96 (*C*H), 126.66 (*C*H), 124.24 (*C*H), 123.79 (*C*H), 121.95 (*C*H), 120.39 (2 x *C*H), 99.19 (*C*H), 29.20 (CH_2) and 28.52 (CH_2); *m/z* (ESI-MS) 222.0 $[M+H]^+$.

2-(1,2,3,4-Tetrahydronaphthalen-2-yl)hydrazinecarboxamide (302).



This compound is novel.

Procedure from **301** was used for the formation of **302** as a light yellow oil after flash chromatography (10→100 % v/v methanol/ethyl acetate) (0.04 g, 0.19 mmol, 19 %); ν_{max} 3444, 3288, 3062, 2982, 2930, 2841, 2580, 2384, 2329, 1616, 1486, 1452, 1436, 1345, 1312, 1254, 1238, 1164, 1135, 1071, 1062, 1038, 949, 925, 839, 814, 768, 741 and 723 cm^{-1}; δ_H (400 MHz, MeOD-d_4) 7.11-7.03 (4 H, m, 4 x Ar-*H*), 3.20-3.10 (1 H, m, C*H*$_{(1)}$H$_{(2)}$CH$_2$CH(NH)CH$_2$), 3.02-2.87 (2 H, m, CH$_2$CH$_2$CH(NH)C*H*$_2$), 2.85-2.74 (1 H, m, CH$_{(1)}$*H*$_{(2)}$CH$_2$CH(NH)CH$_2$), 2.65 (1 H, dd, *J* 16.1, 9.0, CH$_2$CH$_2$C*H*(NH)CH$_2$), 2.12-2.01 (1 H, m, CH$_2$C*H*$_{(1)}$H$_{(2)}$CH(NH)CH$_2$) and 1.70-1.57 (1 H, m, CH$_2$CH$_{(1)}$*H*$_{(2)}$CH(NH)CH$_2$); δ_C (400 MHz, MeOD-d_4) 137.29 (*C*), 135.86 (*C*), 130.33 (*C*H), 129.59 (*C*H), 126.89 (*C*H), 126.81 (*C*H), 57.27 (*C*H), 34.87 (*C*H$_2$), 28.49 (*C*H$_2$) and 28.47 (*C*H$_2$); *m/z* (ESI-MS) 206.1 $[M+H]^+$, 228.0 $[M+Na]^+$.

5. References.

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